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GUIDELINES

Wound, Pressure Ulcer and Burn Guidelines (2023)—5: Guidelines for the Management of Lower Leg Ulcers/Varicose Veins, Third Edition Wound/Pressure Ulcer/Burn Guidelines Drafting Committee (Lower Leg Ulcers/Varicose Veins Group)

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ABSTRACT

Guidelines for the management of lower leg ulcers/varicose veins, third edition is a fully revised guideline drafted by the Japanese Dermatological Association Wound/Pressure Ulcer/Burn Guidelines Drafting Committee. They were developed in a systematic and transparent manner with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In the four clinical questions with meta-analyses, ultrasonography, compression therapy, surgical therapy, and sclerotherapy were weakly recommended in the treatment of lower leg ulcers/varicose veins. General information on diagnosis, prevention, assessment, and unconventional treatment of lower leg ulcers/varicose veins was also provided.

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Contents

1 | Chapter 1 General Information

1.1 | Background of the Drafting of Guidelines for the Management of Lower Leg Ulcers/Varicose Veins, Third Edition

Guidelines are documents systematically prepared to support medical experts and patients in making appropriate judgments in particular clinical situations.

With respect to varicose veins, the "Clinical Practice Guidelines for Endovenous Thermal Ablation for Varicose Veins 2019" were published by the guideline committee of the Japanese Society of Phlebology in April 2019. However, endovenous thermal ablation is primarily described, as represented by the title name.

The Japanese Dermatological Association (JDA) also announced the 1st edition for lower leg ulcers/varicose veins in November 2011 and a revision in 2017. Concerning the contents, the diagnosis of lower leg ulcers, examination of the etiology, therapeutic strategies, and treatment methods are described, but an important item for lower leg ulcer treatment, compression therapy, is also concretely explained. Furthermore, we aim to make the present guidelines function as a tool for improving the quality of medical care for individual patients with lower leg ulcers/varicose veins by systematically presenting data that support clinical decisions for the prevention of lower leg ulcers/varicose veins, care, and treatment based on evidence so that the management of lower leg ulcers/varicose veins in Japan may be improved.

1.2 | Position of the Guidelines for the Management of Lower Leg Ulcers/Varicose Veins

The Wound/Pressure Ulcer/Burn Guidelines Drafting Committee was composed of members delegated by the Board of Directors of JDA. The committee held the start-up meeting on June 3, 2018, and the following face-to-face or online meetings, and drafted six skin wound-related guidelines, including the Guidelines for lower leg ulcers/varicose veins, third edition by taking into consideration the opinions of the Scientific committee and the Board of directors of JDA.

The present guidelines reflect the current standards for management of lower leg ulcers/varicose veins in Japan. The factors that may affect the management of lower leg ulcers/varicose veins are more diverse than those of other skin ulcers; not only the patient's conditions but also the related conditions of his home, families, care providers, and communities may deeply affect the decision in the treatment of lower leg ulcers/varicose veins. The optimal treatment designed for an individual patient will usually be different, if partly, from that recommended in these guidelines. Discordance from the guidelines should not be used in legal disputes. Also, it should be noted that these guidelines have often been quoted in lawsuits in spite of the intention of the guideline committee.

1.3 | Major Update Points in the Third Edition

- In order to make recommendations in a systematic and transparent manner, we developed the guidelines according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, GRADE Handbook, updated October 2013.
- A quantitative systematic review (meta-analysis) was carried out with respect to four clinical questions, namely, ultrasonography, compression therapy, surgical therapy, and sclerotherapy, which the committee members considered clinically most important.
- For the convenience of readers, the outline of management of lower leg ulcers/varicose veins appeared at the top of the guidelines, and the details appeared in the following pages.

1.4 | Financial Support

All expenses required for drafting the guidelines were provided by JDA. Financial or any form of support was not provided by organizations, enterprises, or pharmaceutical companies.

1.5 | Conflicts of Interest (COI)

According to the JAMS Guidelines on COI Management in Medical Research (https://jams.med.or.jp/guideline/index.html) published by the Japanese Association of Medical Sciences in March 2017, the drafting committee members disclosed COI within the 3 years preceding the publication of the guidelines. COI of the following were self-reported by the members to the committee: (1) the committee members and their spouses, (2) the first-degree relatives of the committee members and those who share the household with the committee members, and (3) organizations or departments to which the members belong

1.6 | Literature Search

The systematic review team for each clinical question (CQ) carried out a preliminary search according to the Minds Handbook for clinical practice guideline development 2020. The final literature search was carried out by the Japan Medical Library Association.

- Database search: PubMed, Cochrane Library, Japanese Medical Abstracts Society.
- Publication period: Between January 1980 and December 2020.

1.7 | Systematic Review Methods

Systematic reviews were carried out according to the Minds Manual for Guideline Development 2020 ver. 3.0, with its working templates.

1.7.1 | Evaluation of Studies

The studies retrieved in the literature search were analyzed for their effects and certainty of evidence by systematic review teams. The effects, prepared as Risk Ratio or Risk Difference, and Certainty (strength) of evidence, determined by Limitation in study design or performance (Risk of bias), Inconsistency of results, Indirectness of evidence, Imprecision, and Publication bias, were summarized in the Body of evidence and grouped by outcomes. Randomized trials and observational studies were summarized separately.

1.7.2 | Overall Evidence

The body of evidence integrated across outcomes and the certainty of evidence were unified in Overall evidence. Then, Risk of bias and Indirectness of evidence were reevaluated, and Inconsistency of results, Imprecision, and Publication bias were assessed. Certainty of evidence was classified, as shown in Table 1.

1.7.3 | Quantitative Systematic Review (Meta-Analysis)

When the several studies revealed the similar design and high-degree similarity in their Population, Intervention, Comparison, Outcome (PICO), a meta-analysis was carried out to integrate the results of the studies quantitatively. The results of the meta-analysis served as factors to determine the certainty of evidence.

1.7.4 | Preparation of Summary of Findings Table

For each CQ, the results of the systematic reviews, certainty of evidence, and the balance of favorable effects (benefits)/unfavorable effects (risks and burdens) were summarized in the Summary of Findings table and presented to the Guideline panels.

1.8 | Determining Direction and Strength of Recommendations by Guideline Panels

Guideline panels re-evaluated the Summary of Findings table based on the importance of outcomes and certainty of evidence. Direction and strength of recommendation were voted anonymously for one of the following options:

- Strong recommendation for intervention.
- Weak recommendation for intervention (proposal or conditional recommendation).
- Weak recommendation against intervention (proposal or conditional recommendation).
- Strong recommendation against intervention.

Delphi method for voting was adopted. The recommendation was determined by agreement of more than 80% of the vote. If agreement of more than 80% was not reached in three consecutive votings, the result of voting was regarded as "no recommendation", and the voting panels may not express any recommendations.

TABLE 1 | Certainty (strength) of the body of evidence.

A (strong)	There is strong confidence in the estimated value of effect
B (moderate)	There is moderate confidence in the estimated value of effect
C (weak)	Confidence in the estimated value of effect is limited
D (very weak)	There is little confidence in the estimated value of effect

Immediately before voting on each CQ, the presence or absence of COI was reconfirmed for the panel members. The voting count appeared along with the recommendations.

1.9 | CQ Modification in Preparing the Guidelines

Any of the CQ were not modified in preparing the guidelines.

1.10 | Time Course of Drafting the Guidelines

The Wound/Pressure Ulcer/Burn Guidelines Drafting Committee held the start-up meeting on June 3, 2018, and the following face-to-face or online meetings, and drafted six skin wound-related guidelines during the COVID-19 pandemic era. Guideline panels held the online meeting on December 1, 2022, and voted for the direction and strength of recommendation. The drafts were prepared by the committee members and evaluated by the members of JDA.

Committee for preparing the guidelines for the management of lower leg ulcers/varicose veins (3rd edition)

	Name	Affiliation, profession	Apportionment
Chairman of the supervising committee	Takao TACHIBANA	Department of Dermatology, Hoshigaoka Medical Center, physician	Supervision
Vice-chairman of the supervising committee	Minoru HASEGAWA	Department of Dermatology, University of Fukui, physician	Supervision
Vice-chairman of the supervising committee	Manabu FUJIMOTO	Department of Dermatology, Osaka University, physician	Supervision
Supervising members	Yoshihide ASANO	Department of Dermatology, Tohoku University, physician	Supervision
	Takeshi NAKANISHI	Department of Dermatology, Meiji University of Integrative Medicine, physician	Supervision
	Hiroshi FUJIWARA	Department of Dermatology, Niigata University, physician	Supervision
	Sei-ichiro MOTEGI	Department of Dermatology, Gunma University, physician	Supervision
	Yuichiro YOSHINO	Department of Dermatology, Japanese Red Cross Kumamoto Hospital, physician	Supervision
Representative of the drafting committee	Takeo MAEKAWA	Department of Dermatology, Jichi Medical University Saitama Medical Center, physician	Supervision, Outline/CQ explanation writing, panel meeting
Drafting committee	Takaaki ITO	Department of Dermatology, Hyogo Medical University, part-time physician	Outline, panel meeting
	Takeo IDEZUKI	Department of Dermatology, NTT Medical Center Tokyo, physician	Outline/CQ explanation writing, panel meeting
	Mayumi OTA	Department of Dermatology, The Jikei University School of Medicine, physician	Outline/CQ explanation writing, panel meeting
	Hiroshi SAKAI	Department of Dermatology, Osaka University, physician	Outline/CQ explanation writing, panel meeting
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	Takamitsu TANAKA	Department of Dermatology, Teikyo University, physician	Outline/CQ explanation writing, panel meeting
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	Koji MAKINO	Department of Dermatology, National Hospital Organization Kumamoto Medical Center, physician	Outline/CQ explanation writing, panel meeting
	Hiroshi YATSUSHIRO	Department of Dermatology, Fukui-ken Saiseikai Hospital, physician	Outline/CQ explanation writing, panel meeting
	Akiyo KONDO	Nurse, NTT Medical Center Tokyo, Wound, Ostomy, and Continence Nurse, Compression Stocking Fitter	Panel meeting

	Systematic review team	Panel meeting members
CQ1	Hiroshi SAKAI, Hiroyuki NIIHARA, Takamitsu TANAKA	Takaaki ITO, Takeo IDEZUKI, Mayumi OTA, Yasuko SARAYAMA, Takayuki FUSUMAE, Takeo MAEKAWA, Koji MAKINO, Hiroshi YATSUSHIRO, Akiyo KONDO

	Systematic review team	Panel meeting members
CQ2	Koji MAKINO, Takeo IDEZUKI	Takaaki ITO, Mayumi OTA, Hiroshi SAKAI, Yasuko SARAYAMA, Takamitsu TANAKA, Hiroyuki NIIHARA, Takayuki FUSUMAE, Takeo MAEKAWA, Hiroshi YATSUSHIRO, Akiyo KONDO
CQ3	Takeo MAEKAWA, Hiroshi YATSUSHIRO, Takayuki FUSUMAE	Takaaki ITO, Takeo IDEZUKI, Mayumi OTA, Hiroshi SAKAI, Yasuko SARAYAMA, Takamitsu TANAKA, Hiroyuki NIIHARA, Koji MAKINO, Akiyo KONDO
CQ4	Yasuko SARAYAMA, Mayumi OTA	Takaaki ITO, Takeo IDEZUKI, Hiroshi SAKAI, Takamitsu TANAKA, Hiroyuki NIIHARA, Takayuki FUSUMAE, Takeo MAEKAWA, Koji MAKINO, Hiroshi YATSUSHIRO, Akiyo KONDO

1.11 | Drafting Committee Members of the Diagnosis and Treatment of Pressure Ulcers, Third Edition

Refer to Drafting-committee member list in Appendix 1.

1.12 | Public Review Prior to Publication

Prior to the publication, public opinions for the guidelines were invited from the members of JDA between 2022 and 2023. The guidelines were revised through the discussion in the committee.

1.13 | Promotion of the Guideline After Publication

The guidelines were presented in the General meeting of JDA, and published in the *Japanese Journal of Dermatology*. The online version of the guidelines is freely downloadable from the JDA website. The publication of its English version is forthcoming.

1.14 | Plans for Revision

The present guidelines are scheduled to be revised in 5 years. If necessary, the update will be presented on the JDA website.

1.15 | Evaluation of the Effects of Guidelines

After the publication, utilization and clinical impact of the guidelines will be surveyed.

1.16 | Summary of Recommendations

CQ1 Is ultrasonography recommended for the diagnosis of venous leg ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform ultrasonography for the diagnosis of venous leg ulcers	Weak	Very weak

CQ2 Is compression therapy recommended for the treatment of venous leg ulcers associated with primary or secondary varicose veins?

Recommendation	Strength	Certainty of evidence
We propose to perform compression therapy for venous leg ulcers associated with primary or secondary varicose veins.	Weak	Very weak

CQ3 Is surgical therapy recommended for the treatment of venous leg ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform stripping of the saphenous vein/high ligation or endovenous thermal ablation (laser, radiofrequency) for the treatment of venous leg ulcers associated with primary varicose veins.	Weak	Very weak

CQ4 Is sclerotherapy recommended for the treatment of venous leg ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform sclerotherapy for venous leg ulcers associated with varicose veins.	Weak	Very weak

2 | Chapter 2 Outline of the Management of Lower Leg Ulcers/Varicose Veins

2.1 | Diagnostic and Therapeutic Algorithm of Lower Leg Ulcers/Varicose Veins

The basic principle informing the design of the present Guidelines is to assist the differential diagnosis of disturbances of venous return, which are the predominant cause of lower leg ulcers, and the selection of appropriate treatment. In venous ulcers of the lower leg, it is important to treat the cause, venous stasis (venous hypertension). Therefore, while our algorithm includes compression therapy as the most important element, it also shows the selection of surgery and sclerotherapy for primary varices, and the necessity of strict compression therapy for secondary varices. Figure 1 shows a diagnostic and therapeutic algorithm based on the above basic principle.

2.2 | Disease Concept

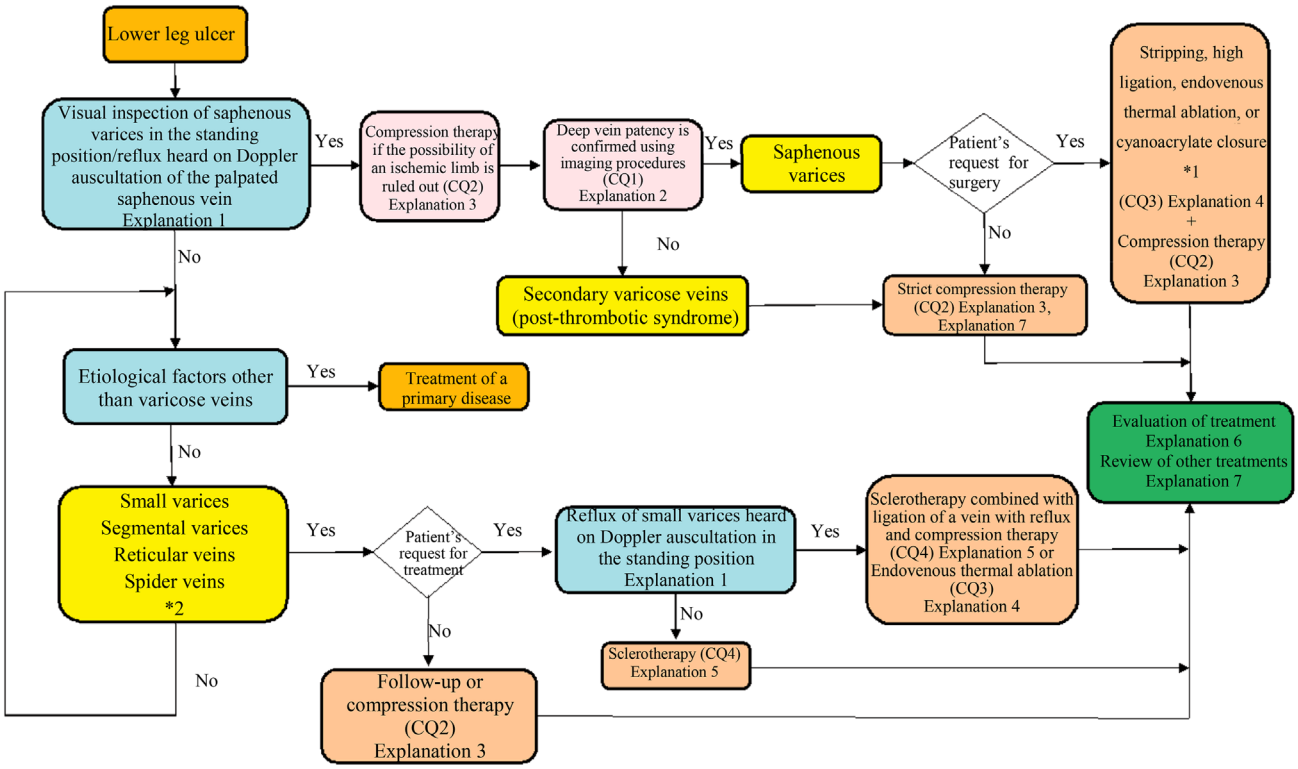
The definition of "lower leg ulcer" is not clear, but it is a general term for ulcers that occur in the lower leg. It refers to a condition in which an ulcer involving the area from knee to the dorsum of the foot. This condition is associated with various etiological factors, but is related to venous insufficiency, such as primary or secondary varicose veins, in many cases, excluding trauma and burns. In untreated patients or those followed-up after topical therapy alone, lower leg ulcers are refractory.

Varicose veins are defined as "a condition in which superficial veins of the leg are markedly dilated/curved/tortuous". Most varicose veins are caused by insufficiency of a venous valve that prevents blood reflux. Cases in which this change in the superficial vein is etiologically associated with the vein itself are termed primary varicose veins. Cases in which this change is related to an etiological factor other than the regional vein are termed secondary varicose veins.

2.3 | Epidemiology

There are no accurate data on the number of patients with varicose veins in Japan, but varicose veins were observed in 8.6% of 9123 subjects aged ≥40 years (mean age: 62.4 years) (males: 3.8%, females: 11.3%) according to the results of a survey in 2005 published by Konishi et al., Department of Epidemiology and Preventive Medicine, Ehime University School of Medicine. Based on the survey results, it is estimated that there may be more than 10 million patients with varicose veins in Japan [2]. A survey of 2000 randomly selected adults in France revealed varicose veins in 30.1% of males and 50.5% of females (2004) [3].

According to a survey in 2404 residents in San Diego (United States) reported in the American Venous Forum guidelines that varicose veins were observed in 24.2% of adults (males: 15.9%, females: 28.5%). Concerning racial differences, Caucasians accounted for 25.3%, Blacks for 20.7%, Hispanics for 27.2%, and Asians for 19.2%. In Asians, varicose veins were less frequent than in Caucasians (2003) [4].



*1: If the ulcer is large, split-thickness skin grafting should be performed at the same time as varicose vein surgery or later.
*2: As small varicose veins alone rarely induce lower leg ulcers, it is necessary to investigate etiological factors other than venous ones.

FIGURE 1 | Diagnostic and therapeutic algorithm of lower leg ulcers/varicose veins (excluding congenital varices). Modified from Ito et al. [1].

With respect to venous thromboembolism (VTE) as an etiological factor for secondary varicose veins, the annual total incidence of pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT) in Europe and the United States is 104 to 183 per 100000 persons (2016). In the United States, the incidence is the highest in African Americans, followed by European/Hispanic and Asian Americans [5]. In Japan, the incidences of PTE and DVT were 12.6 and 19.2 per 100000 persons, respectively (2018), which are markedly lower than in Europe and the United States. However, these numbers have slightly increased annually [6].

In Japan, guidelines for the prevention of VTE were published in 2004. With the widespread use of preventive strategies in inpatients, the incidence of perioperative PTE has decreased [7]. However, the PTE-associated mortality rate in untreated patients is approximately 30% in Europe and the United States, and that within 30 days in patients receiving adequate treatment is 1.8%. In Japan, the VTE-associated mortality rate within 30 days is reportedly 1.6% [8]. The mortality rate remains high, emphasizing the importance of preventive strategies. The incidence of VTE increases with age. Regarding sex, the ratio of males to females is slightly higher (males:females = 1.2:1) in Europe and the United States, while in Japan, the ratio is higher for females(1:1.4 to 1:1.8) [9].

On the other hand, the definition of lower leg ulcers is not clear. In Japan, lower leg ulcers correspond to L97 "leg ulcer conditions that are not classified as others" in the disease name code "ICD10". This code include several causative diseases, but the details remain unclear.

2.4 | Wound Healing Process and Its Disturbance (Details Appeared in 3 and 4)

Venous ulcers of the lower leg occur due to venous hypertension in the area at adjacent to the ulcer, which is related to venous insufficiency in the leg. Primary varicose veins are primarily associated with valve insufficiency of the saphenous vein or venous reflux from incompetent perforating veins. As for the etiology of secondary varicose veins, venous hypertension related to deep venous insufficiency or deep venous valve insufficiency delays wound healing, making lower leg ulcers refractory. Ulcer healing may be achieved by reducing venous hypertension. Therefore, compression therapy involving the foot and the entire leg should initially be performed using elastic bandages or stockings after cleaning the ulcer site and placing non-adhesive gauze. If there is no arterial occlusive disease, such as limb ischemia, compression therapy should be performed regardless of the ulcer etiology, whether from primary or secondary varicose veins. This may lead to ulcer healing.

When ulcers are complicated by infection, local treatment for infection and the administration of antimicrobial drugs can promote healing. The use of topical agents for ulcers slightly shortens the tome to healing, but the primary purpose of treatment is to reduce venous hypertension. Without adequate compression therapy, ulcer healing may not be achieved. For primary varicose veins, surgical therapy is effective because it reduces venous blood pressure in the lower leg (Explanation 4). However, in case of secondary varicose veins, it is often difficult to treat the underlying causes, so compression therapy to reduce superficial venous pressure should be performed as symptomatic therapy (Explanation 3).

2.5 | Diagnosis of Lower Leg Ulcers/Varicose Veins (1 and 2, CQ1)

If an ulcer is present on the lower leg, a diagnosis of a lower leg ulcer can be made. Around venous insufficiency-related lower leg ulcers (1.1), so-called "stasis dermatitis", venous hypertension-related dermatitis, and post inflammatory lesions, such as pigmentation are observed in many cases.

Most ulcers located on the upper medial malleolus or anterior surface of the leg are associated with reflux of the great saphenous vein, while many ulcers on the upper lateral malleolus are associated with reflux of the small saphenous vein. Some studies have reported that these locations correspond to areas where incompetent perforating veins frequently occur, through other studies emphasize that there is no such relationship. When circumferential ulcers or dermatitis are observed, the condition is often associated with reflux of both the great and small saphenous veins, deep venous valve insufficiency, or post-thrombotic syndrome.

Venous ulcers rarely involve the dorsum of the foot to dorsum of toes and do not occur on the sole of the foot or tiptoes. For diagnosing lower leg ulcers or varicose veins, it is necessary to have the patient stand and perform visual inspection and palpation of the entire leg, ensuring that the inguinal region and base of the femur are not compressed by clothing. Otherwise, it may be difficult to make an accurate diagnosis (it is recommended to prepare a wrap skirt for diagnostic purposes). Even in a sitting position (in a chair), lower leg ulcers or varicose veins can be overlooked. In the supine position on an examination table, venous dilation, curve or tortuosity ma not be detectable during visual inspection. Furthermore, diagnosis may be impossible even in the standing position if superficial veins in the femoral region are compressed by tucked-up pants (1.3).

For diagnosis varicose veins, ultrasonography is necessary (CQ1). If Doppler auscultator or duplex ultrasonography reveals reflux of superficial veins, a diagnosis of varicose veins can be made (1.4). Additionally, ultrasonography can confirm details of varicose veins, patency of deep veins, and the presence of a thrombus in many cases. If deep vein thrombosis is suspected, its location can be diagnosed by measuring the D-dimer level and performing venous-phase contrast-enhanced CT. In acute cases, emergency contrast-enhanced CT is necessary. In some institutions, the venous along the entire length of the leg can be evaluated using MRV (vein visualization using MRI or MRI venography) (2.2). Even severely affected veins can often be diagnosed with this method.

Most of the above examination methods assess venous morphology, but a physiological function test for leg veins, such as air plethysmography (APG), can facilitates the evaluation of venous dynamics.

2.6 | Clinical Classification (2.1)

Usually, lesions are classified according to the CEAP classification (Table 3 in Chapter 4).

2.7 | Treatment of Lower Leg Ulcers/Varicose Veins (3 to 5 and 7, CQs2 to CQ4)

For lower leg ulcers related to venous hypertension, compression therapy with elastic bandages/stockings should be performed regardless of etiology (CQ2, Explanation 3). If varicose veins are diagnosed in the standing position and arterial occlusion is ruled out by palpation of the leg arteries or ankle brachial pressure index measurements, compression therapy may be started at the initial consultation.

Surgical treatment is recommended for lower leg ulcers associated with primary varicose veins when the patency of deep veins is confirmed (CQ3, Explanation 4). Stripping was previously the standard procedure, yielding favorable postoperative outcomes (4.1). Additionally, high ligation can block reflux in the great saphenous vein, but it does not prevent reflux from the femoral perforating or accessory saphenous veins; thus, collateral flow may develop over time. Consequently, high ligation alone or combined with trunk sclerotherapy (CQ4, Explanation 5) is advised. However, recurrence is often observed despite these treatments.

Recently, endovenous thermal ablation (e.g., laser or radiofrequency ablation) has gained popularity as a new surgical technique, with studies indicating that its postoperative outcomes are comparable to stripping (4.2). However, tumescent local anesthesia (TLA) is required for this technique.

Cyanoacrylate closure, covered by health insurance since 2019, is the latest technique and does not require anesthesia for venous occlusion. Given the limited number of patients treated with this method, long-term postoperative follow-up is necessary to assess outcomes. Treatment results for varicose veins using this method are similar to those achieved with conventional stripping (4.3). However, no prospective studies have evaluated cyanoacrylate closure specifically for lower leg ulcers. Furthermore, complications related to thrombus formation, allergic reactions to cyanoacrylate, and foreign body-related infections may arise, necessitating careful postoperative monitoring.

Treatment choices should be informed by the "Clinical Practice Guidelines for Endovenous Thermal Ablation for Varicose Veins 2019" (*Phlebology* 2019; 30 Suppl: i-81), edited by the Japanese Society of Phlebology Guideline Committee and supervised by the Japanese Society of Phlebology, and "Cyanoacrylate Glue Closure for Varicose Veins: Consensus Guidelines of the Japanese Society of Phlebology" (*Phlebology* 2020; 31: 141–152).

Other reported treatments include Kampo (Japanese herbal) medicines such as Keishibukuryogan and Shakuyakukanzoto, which are used to relieve symptoms, including cramps, in patients with primary varicose veins or DVT (Explanation 7).

2.8 | Evaluation of Treatment (Explanation 6)

In some cases, adequate treatment does not relieve symptoms, and lesions may recur after initial symptom relief; therefore, both subjective and objective evaluations are necessary post-treatment. For subjective evaluation, the best parameter is the improvement in symptoms or complaints after treatment compared to pre-treatment (6.1). For objective evaluation, auscultation for superficial venous reflux with a Doppler device (6.2) and imaging confirmation using color Doppler ultrasonography (6.3) are useful. Additionally, serial assessment of hematological parameters, such as D-dimer levels, along with imaging, is helpful in evaluating post-thrombotic syndrome (PTS) (6.4).

2.9 | Posttreatment Follow-Up

A key factor in ulcer healing is the adequacy of compression therapy. If primary varicose veins are suspected, surgery should be considered after confirming deep vein patency through imaging procedures. Surgical intervention for varicose veins can reduce the healing time for ulcers, with the exception of cases where only sclerotherapy for small varicose veins is performed.

However, varicose vein surgery does not address all superficial veins; thus, to reduce reflux in residual branch veins, compression therapy should continue for several weeks post-surgery. Even if reflux in the treated saphenous vein is entirely controlled, accessory saphenous veins may remain, and varicose veins can recur due to reflux through these veins. Surgery or compression therapy alone cannot entirely prevent the recurrence of leg varicose veins. Additionally, in patients with primary varicose veins, incompetent perforating veins may contribute to recurrence if deep venous valve insufficiency persists post-surgery.

In patients with deep venous valve insufficiency who have undergone full-length stripping of the great or small saphenous veins—a procedure now less commonly performed—ulcers may develop on the dorsum of the foot and toes in the late phase, becoming difficult to treat. In such cases, 5-toe compression socks may promote ulcer healing or reduction.

3 | Chapter 3 Clinical Questions (CQs) and Recommendations

CQ1 Is Ultrasonography Recommended for the Diagnosis of Venous Leg Ulcers?

Recommendation	Strength	Certainty of evidence	Voting count
We propose to perform ultrasonography for the diagnosis of venous leg ulcers.	Weak	Very weak	Varicose veins, 9/9, Deep vein thrombosis, 9/9

3.1 | Background

Many lower leg ulcers are associated with chronic venous insufficiency (CVI) due to impaired venous return. Additionally, the affected vein can often be predicted based on a history of CVI, characteristic clinical features, and ulcer location; however, a detailed examination of the specific causative vein is necessary for effective treatment. We evaluated the diagnostic capacity of ultrasonography for identifying causative veins, using color Doppler-combined duplex ultrasonography and compression ultrasonography, where the vein is compressed with a probe to detect thrombus.

3.2 | Objectives

In order to assess the efficacy of ultrasonography in diagnosing venous leg ulcers, systematic reviews were conducted.

3.3 | Results

CVI-associated venous lesions of the leg primarily include varicose veins and deep vein thrombosis (DVT). Standard evaluation methods for varicose veins and DVT have been collaboratively established by three societies: the Japan Society of Ultrasonics in Medicine, the Japanese College of Angiology, and the Japanese Society of Phlebology [11].

The presence or absence of valve insufficiency in varicose veins can typically be evaluated by inducing blood flow through peripheral milking of the measurement site or by using the Valsalva maneuver, and measuring the reflux time with pulse Doppler ultrasonography. However, in patients with extensive deep vein insufficiency, those with suspected or known DVT, or those with complex recurrence after high ligation, venography of the leg is sometimes required. Venography may also be necessary for genital varicose veins, or in cases where color Doppler ultrasonography provides unusual findings or cannot accurately assess varicose vein structure due to atypical distribution [12]. In addition, ultrasonography alone may be insufficient for diagnosing intrapelvic lesions [13]. No randomized controlled trial (RCT) has compared the diagnostic accuracy of venography with that of ultrasonography for varicose veins; hence, the recommendation for CQ1 was reviewed, with a focus on DVT.

In terms of ultrasonography's efficacy in diagnosing DVT, there are eight meta-analyses [14–21], two systematic reviews [22, 23], and twelve prospective studies [24–35]. Based on these systematic reviews, the sensitivity of ultrasonography for DVT diagnosis ranges from 31.1% to 97%, and its specificity ranges from 63% to 100%. Differences in diagnostic accuracy are influenced by examiner skill, examination technique (duplex or compression methods), patient selection (presence or absence of symptoms), and DVT location. Some studies found no significant difference in results compared to venography [34, 35]. Furthermore, multiple ultrasonography sessions can improve the diagnosis rate [36], and combining ultrasonography with D-dimer or fibrinogen assessments may enhance diagnostic accuracy [37].

However, one study reported a 50% rate of overlooked asymptomatic DVT cases [16]. Other studies showed that ultrasonography's diagnostic accuracy was approximately 80% compared to venography [27], which remains insufficient [33]. Additionally, diagnosing chronic-phase DVT can be challenging, even with imaging procedures [38, 39]. If ultrasonography results are inconclusive or if DVT symptoms are present without abnormal ultrasound findings, venography should be performed [32].

3.4 | Further Information

For detailed examination of venous leg ulcers, ultrasonography is recommended. Diagnosing varicose veins is most reliable with the patient in the standing position. Even if a diagnosis is difficult in the sitting or supine position, the standing position examination often yields clearer results. Since Sigel et al. [40] compared Doppler findings with venography findings in 1967, the utility of Doppler auscultation in diagnosing venous insufficiency has been recognized. Koyano et al. [41] also reported a 72%–96% consistency between Doppler findings and venography, a conventional gold standard. Doppler auscultation has since become a widely used, noninvasive diagnostic method for venous insufficiency, which is the most common cause of lower leg ulcers. It is recommended as a screening method due to its simplicity and standard use in outpatient care.

Concerning concrete methods of testing with a Doppler auscultator, retrograde blood flow is induced using the lower leg milking method in the standing position (manual compression and release) or Valsalva method in severe cases. If superficial vein reflux sounds are heard, a diagnosis of varicose veins or superficial vein valve insufficiency can be made, or secondary varicose veins should be suspected if consecutive upward sounds are heard on auscultation with a probe immediately above the small saphenous vein [40]. In some cases of old secondary varicose veins, superficial vein blood flow sounds are not heard on auscultation with a Doppler auscultator [42]. In such cases, it is necessary to confirm the presence or absence of deep vein thrombosis by testing. A study reported that Doppler auscultation facilitated the accurate, ultrasonography-free diagnosis of venous insufficiency in typical patients [43]. An RCT showed that both the sensitivity and specificity of Doppler auscultation for confirming superficial vein reflux were similar to those of ultrasonography [44].

The diagnosis of varicose veins using the above Doppler auscultation method is possible in most cases, but it is difficult to evaluate deep veins, and morphological diagnosis is difficult. On the other hand, the duplex method facilitates the morphological assessment of superficial vein blood flow. The morphological and functional diagnosis of superficial/deep veins and perforators is also possible. In particular, the duplex method has merits: it is noninvasive and inexpensive, and real-time observation is possible. This examination method is considered to be the most useful [45, 46]. Considering the bias risk of RCT, the strength of total evidence was set at D (very weak), and the recommendation level was established as weak at a panel meeting.

3.5 | Precautions for Clinical Use

The usefulness of ultrasonography for detecting varicose veins or DVT in the leg is well established as a standard examination, and it should routinely be performed for diagnosis. In this CQ, the recommendation level is weak, as no prospective RCT has been conducted due to the established nature of the examination procedure and because blinding is impractical given the examination method.

Post-thrombotic syndrome (PTS) after DVT is a common cause of secondary varicose veins. However, clinical symptoms are absent in some patients with DVT [47], and DVT may not have been diagnosed. Thus, while careful attention to the patient's medical history is essential, confirming deep vein patency with imaging procedures is necessary. Furthermore, physicians should be adequately skilled in interpreting ultrasonography findings, particularly concerning deep vein anatomy. If visualization is challenging with ultrasonography, venography, venous-phase contrast-enhanced CT, or MRV should be considered. Additionally, CVI can occur in patients with intrapelvic tumors, heart failure, renal failure, or obesity; therefore, a thorough examination is required even in the absence of clear venous return disturbance.

3.6 | Possibility of Future Research

It is necessary to examine the type of patients in whom ultrasonography is insufficient. In addition, there is no obvious parameter reflecting the necessity of venography, venous-phase contrast-enhanced CT, or MRV, and evidence should be accumulated.

CQ2 Is Compression Therapy Recommended for the Treatment of Venous Leg Ulcers Associated With Primary or Secondary Varicose Veins?

Recommendation	Strength	Certainty of evidence	Voting count
We propose to perform compression therapy for venous leg ulcers associated with primary or secondary varicose veins. However, caution is needed so that there may be no overpressure in ischemic limbs	Weak	Very weak	9/9

3.7 | Background

In the presence of varicose veins, venous hypertension in the leg occurs. When vascular permeability is chronically enhanced, leakage of fibrinogen or erythrocytes induces chronic inflammation, leading to hemosiderin deposition, connective tissue outgrowth, and sclerosis. Furthermore, venous hypertension in the leg inhibits arterial blood inflow, affecting tissue nutritional status. Venous ulcers of the lower leg, which account for the majority of lower leg ulcers, develop due to further reduction in barrier function and weakened resistance to external stimuli, making them refractory. Compression with elastic bandages or stockings to relieve venous hypertension in the leg is essential for treating venous ulcers. Our aim is to examine the effects of compression therapy on venous ulcers of the lower leg using the EBM method and confirm the importance of this therapy.

3.8 | Objectives

In order to assess the efficacy of compression therapy for venous leg ulcers, systematic reviews were conducted.

3.9 | Results

We reviewed literature verifying the usefulness of compression therapy for venous leg ulcers associated with primary or secondary varicose veins. We adopted three RCTs [48–50] comparing the compression therapy group with the compression therapy-free group, establishing the ulcer-healing rate as an outcome, as well as one RCT [51] that established the recurrence rate as an outcome. A quantitative systematic review was performed, establishing the ulcer-healing rate as the outcome.

3.10 | Further Information

There are four RCT [48–51] on compression therapy for venous leg ulcers. A quantitative systematic review of three RCTs [48–50] comparing the healing rate of venous leg ulcers between compression therapy and compression therapy-free groups was performed. Among 79 patients in the compression therapy group, ulcer healing was achieved in 42 (ulcer-healing rate: 53.2%). In the compression therapy-free group of 80 patients, it was achieved in 25 (31.3%) (RR 4.00, 95% CI [2.03–7.85], $Z = 4.02$, $p < 0.0001$). A significant difference in the ulcer-healing rate was observed between the two groups. In an RCT by Vandongen et al. [51], the recurrence rate of ulcers in the compression-free group after compression therapy was significantly higher than in the compression group (56% vs. 31%, $p < 0.001$).

Compression therapy for venous leg ulcers leads to earlier improvement than in the compression-free group, increasing the healing rate [48–50, 52]. When compression therapy is continued after healing, the recurrence rate decreases [51, 53]. Additionally, recurrence increases with reduced patient compliance to compression therapy [54]. Therefore, the importance of compression therapy should be emphasized to patients after ulcer healing, and it should be continued.

However, RCTs carry a bias risk, and blinding is difficult when comparing ulcer healing and recurrence rates. Consequently, the bias risks for these parameters are high, and the strength of the overall evidence is very weak. The recommendation level was therefore rated as weak at a panel meeting.

Venous leg ulcers occur due to venous hypertension in areas adjacent to the ulcer site, related to leg venous insufficiency,

and ulcer healing is achieved by relieving this condition. Compression therapy, from the foot to the entire leg, should initially be applied using elastic bandages or stockings. Its mechanisms include "enhancing pumping actions related to the repulsion force between the muscle and compression," "reducing vein diameter and increasing venous flow velocity," "reducing venous reflux," "improving edema and microcirculation by decreasing leakage and increasing reabsorption," and "reducing inflammatory cytokines from peripheral cells." [55] When effective, these actions may alleviate venous hypertension, promoting venous ulcer improvement. If arterial obstructive disease, such as foot ischemia, is absent, compression therapy may promote ulcer healing. Furthermore, at bedtime in the supine position, venous pressure at the ulcer site reduces to near central venous pressure levels, allowing compression removal.

Ulcers associated with primary and secondary varicose veins gradually decrease. However, in surgical cases, treating secondary varicose vein causes is often challenging, necessitating compression therapy to reduce superficial venous pressure. A limitation of compression therapy is the difficulty of consistent use with compression braces (bandages or stockings), as application requires finger strength. Additionally, pressure pain at the ulcer site may occur during application. With stockings, shear stress may cause pain, even with non-adhesive gauze on the wound site. Stocking use can also be inconvenient, making sustained compression therapy challenging in many cases.

Lower leg ulcers associated with post-thrombotic syndrome (PTS) are also refractory, but strict compression therapy may improve mild to moderate cases [56]. In severe cases, strict compression therapy may lead to improvement but requires higher pressure [56]. Furthermore, continuous compression therapy after DVT onset significantly reduces PTS incidence [57].

3.11 | Precautions for Clinical Use

Compression therapy is a basic treatment for venous leg ulcers to be performed as widely as possible. However, if peripheral artery disease (PAD) is present, compression therapy may lead to limb ischemia. Therefore, if the ankle brachial index (ABI) suggests arterial blood flow disturbance, compression therapy must be performed carefully to avoid overpressure or uneven pressure distribution. In patients with an ABI of <0.8, the indication for this therapy should be carefully evaluated. A study reported that venous return could be improved without inhibiting arterial blood flow by using a foot pump when the ABI was <0.8 [58]. Furthermore, it is recommended that arterial blood flow be evaluated using Doppler auscultation of the posterior tibial and interdigital arteries before and after compression therapy.

For compression therapy, elastic bandages/stockings are used. However, as described in Chapter 4 (4.2 Definitions of terminology), it is essential to ensure that adequate pressure is achieved using appropriate materials. Regarding bandages, less stretchable, highly elastic bandages are more effective than highly stretchable, less elastic standard bandages. Furthermore, therapeutic effects vary depending on the compression pressures at the ankle; therefore, one of the pressures listed in Table 2 should be selected according to the condition. Compression pressure at the ankle can be measured using a special device. Even when elastic stockings are used, the ankle pressure should be selected based on the condition being treated, as described for elastic bandages. Elastic stockings are highly elastic and sometimes difficult to put on; therefore, tools such as stocking donners or rubber gloves can be helpful. Moreover, the recurrence rate of skin lesions is lower with higher compression pressure, but patient compliance decreases with high compression pressure. Therefore, to effectively alleviate venous leg ulcers and prevent their recurrence, it is crucial to repeatedly educate patients about the importance of compression therapy [58].

CQ3 Is Surgical Therapy Recommended for the Treatment of Venous Leg Ulcers?

Recommendation	Strength	Certainty of evidence	Voting count
We propose to perform stripping of the saphenous vein/high ligation or endovenous thermal ablation (laser, radiofrequency) for the treatment of venous leg ulcers associated with primary varicose veins.	Weak	Very weak	9/9

3.12 | Background

The efficacy of various surgical treatments for primary varicose veins has been established and is not controversial. However, for patients with venous leg ulcers associated with primary varicose veins, criteria for performing surgical treatment in addition

TABLE 2 | Compression pressure at the ankle (unit: MmHg).

<20 mmHg	Prevention of DVT, prevention of varicose veins, after stripping of varicose veins, edema related to other diseases
20–30 mmHg	Mild varicose veins, varicose veins in the elderly
30–40 mmHg	After surgery for varicose veins, after sclerotherapy, mild post-thrombotic syndrome
40–50 mmHg	Varicose veins with lower leg ulcers, varicose veins with marked edema, sequelae of DVT, lymphedema
≥ 50 mmHg	Severe lymphedema

Note: Cited and modified from Sakaguchi [59].

to adequate local treatment and compression therapy have not been established. This study aims to evaluate the effects of various surgical treatments on venous leg ulcers using an evidence-based medicine (EBM) approach and to provide guidance for treatment strategies.

3.13 | Objectives

In order to assess the efficacy of various surgical treatments for venous leg ulcers, a systematic review was conducted.

3.14 | Results

A literature search was performed on various surgical treatments (stripping/high ligation and endovenous thermal ablation) available for primary varicose veins in Japan. Documents validating their usefulness for treating venous leg ulcers associated with primary varicose veins were included.

For stripping/high ligation, a quantitative systematic review was conducted using three RCTs [60–62] comparing these procedures with compression therapy alone, with ulcer-healing rate as the primary outcome. For endovenous thermal ablation, a quantitative systematic review was conducted using two RCTs [63, 64] comparing this procedure with compression therapy alone, with ulcer-healing rate as the primary outcome.

3.15 | Further Information

In this CQ, the ulcer-healing rate was established as the primary outcome to evaluate the efficacy of various surgical treatments for venous leg ulcers associated with primary varicose veins.

Concerning stripping/high ligation, a quantitative systematic review was performed using three RCT [60–62] comparing the ulcer-healing rate between these procedures and compression therapy alone. Among 385 patients treated with compression therapy alone (compression therapy group), ulcer healing was achieved in 323 cases (ulcer-healing rate: 83.9%). Among 362 patients in the therapeutic intervention group, 317 cases were healed (87.6%) (RR 1.04, 95% CI [0.98–1.11], $Z = 1.45$, $p = 0.15$). No significant difference in the ulcer-healing rate was observed between the two groups. However, in an RCT by Gohel et al. [60], the recurrence rate of ulcers 48 months post-treatment was significantly lower in the therapeutic intervention group than in the compression therapy group (31% vs. 56%, respectively, $p < 0.001$). Similarly, in an RCT by Zamboni et al. [61], the recurrence rate of ulcers 3 years post-treatment was significantly lower in the therapeutic intervention group (9% vs. 38%, respectively, $p < 0.005$). In contrast, an RCT by Gent et al. [62] found no significant difference in the recurrence rate 3 years post-treatment between the two groups (22 vs. 23%, respectively). While stripping/high ligation did not result in a statistically significant improvement in ulcer-healing rates, these procedures significantly reduced ulcer recurrence rates and may effectively shorten the duration of venous leg ulcers over the long term. Due to the risk of bias in RCTs, the overall evidence strength was rated as D (very weak), and the recommendation level was determined to be weak.

For endovenous thermal ablation, a quantitative systematic review was performed using two RCT [63, 64] comparing the ulcer-healing rate at 6 months after the start of treatment between this procedure and compression therapy alone. Among 254 patients treated with compression therapy alone (compression therapy group), 196 cases were healed (ulcer-healing rate: 77.2%). In 250 patients from the therapeutic intervention group, it was achieved in 217 cases (86.8%) (RR 1.12, 95% CI [1.04–1.22], $Z = 2.79$, $p = 0.005$). The therapeutic intervention group showed a significantly higher ulcer-healing rate. Due to the risk of bias in RCTs, the overall evidence strength was rated as D (very weak), and the recommendation level was determined to be weak.

3.16 | Precautions for Clinical Use

Surgical treatment is recommended in cases where there is no significant improvement in venous leg ulcers associated with primary varicose veins despite compression therapy, when compression therapy is not feasible, or to reduce the risk of recurrence after venous leg ulcer healing. However, when performing surgery for varicose veins, the advantages and disadvantages of each technique should be explained, and procedures should only be performed after obtaining informed consent from patients.

To perform endovenous thermal ablation under health insurance coverage, both institutional and physician criteria established by the committee for performing/managing endovenous thermal ablation of varicose veins must be met. Additionally, the procedure should be conducted in accordance with the guidelines for endovascular treatment of varicose veins of the leg (*Phlebology* 2019; 30 Supple: i-81) as prepared by the Japanese Society of Phlebology committee.

3.17 | Possibility of Future Research

Regarding cyanoacrylate closure (n-butyl-2-cyanoacrylate), this procedure has recently become available, but there is no direct evidence supporting its efficacy for venous leg ulcers; thus, it was not included in this CQ. However, one study reported that this procedure was as effective as endovenous thermal ablation as a treatment option for primary varicose veins [65]. In a retrospective observational study evaluating the ulcer-healing rate in 37 patients (39 legs) with venous leg ulcers at a single facility, a combination of cyanoacrylate closure and compression therapy resulted in rapid ulcer healing [66]. Therefore, this procedure may also be effective for venous leg ulcers. A prospective study on cyanoacrylate closure for venous leg ulcers should be conducted in the future.

For surgical therapy targeting primary varicose veins, approaches primarily focus on the saphenous vein. However, treating only the saphenous vein trunk has its limitations. In patients with refractory varicose veins, treatment for incompetent perforating veins may be required. Historically, open perforator surgery, in which an incompetent perforating vein is ligated/dissected under direct visualization (Linton surgery), was performed. Subsequently, minimally invasive treatments such as subfascial endoscopic perforator vein surgery (SEPS) or percutaneous ablation of perforators (PAPS) have been developed. High-quality prospective studies are needed to evaluate whether simultaneous treatment

of incompetent perforating veins during saphenous vein trunk treatment improves the healing rate of venous leg ulcers.

CQ4 Is Sclerotherapy Recommended for the Treatment of Venous Leg Ulcers?

Recommendation	Strength	Certainty of evidence	Voting count
We propose to perform sclerotherapy for venous leg ulcers associated with varicose veins.	Weak	Very weak	9/10

3.18 | Background

Most varicose veins as an etiological factor for venous leg ulcers are saphenous varices. Standard treatments for saphenous variceal reflux include various surgical methods, such as stripping, high ligation, endovenous thermal ablation, and cyanoacrylate closure. While sclerotherapy has traditionally been used for small varicose veins, foam sclerotherapy for saphenous varices has recently been employed in some cases. One study reported that foam sclerotherapy was more effective than liquid sclerotherapy [67].

It may be clinically important to determine whether sclerotherapy for saphenous varices is effective for venous leg ulcers associated with varicose veins.

3.19 | Objectives

In order to evaluate the efficacy of sclerotherapy for saphenous varices in venous leg ulcers, a systematic review was conducted.

3.20 | Results

Literature searching was performed, focusing on outcomes such as ulcer-healing rates following sclerotherapy for venous leg ulcers, incidence of complications, and quality of life (QOL) improvements. Two RCTs were identified [68, 69].

One study compared the ulcer-healing rate between compression therapy alone and compression therapy combined with sclerotherapy [68]. After 24 weeks, the healing rates were 85% and 92%, respectively, with no significant difference. Another study compared the ulcer-healing rate between stripping and sclerotherapy, finding no significant difference (100% and 91.3%, respectively) [69].

The incidence of complications in the stripping and sclerotherapy groups was 14.2% and 13.0%, respectively, with no significant difference. No serious complications occurred in either group [69]. Similarly, the other study reported that serious adverse events were rare [68].

Regarding QOL improvement, comparisons were made between the stripping and sclerotherapy groups using the Aberdeen Varicose Vein Questionnaire (AVVQ), Venous Clinical Severity Score (VCSS), and Venous Disability Score (VDS) before and after treatment. There were no significant differences in the improvement of these scores between the two groups [69].

3.21 | Further Information

A qualitative systematic review was conducted to evaluate the efficacy of sclerotherapy for venous leg ulcers associated with varicose veins, focusing on ulcer-healing rates, incidence of complications, and QOL improvements. One article assessed all these factors using the stripping group as a control [69].

Blinding between the sclerotherapy and control groups was challenging. There were no significant differences in ulcer-healing rates, incidence of complications, or QOL improvements between the two groups. Based on these findings, it was determined at a panel meeting that sclerotherapy should be weakly recommended for venous leg ulcers associated with varicose veins.

3.22 | Precautions for Clinical Use

A qualitative systematic review was conducted to evaluate the efficacy of sclerotherapy for venous leg ulcers associated with varicose veins, focusing on outcomes such as the ulcer-healing rate over a specific period, incidence of complications, and QOL improvements. However, the studies included in the review were conducted in other countries. In Japan, the package inserts for polidocanol (Polidocasclerol) indicate that the efficacy and safety of this agent have not been established for primary varicose veins measuring > 8 mm in diameter with liquid sclerotherapy or > 12 mm in diameter with foam sclerotherapy. As a result, its use for such varicose veins is restricted.

Moreover, in the studies analyzed for this CQ, sclerotherapy was always combined with compression therapy. The therapeutic effects of sclerotherapy alone remain unclear.

3.23 | Possibility of Future Research

Recently, the frequency of stripping as a surgical treatment has decreased in Japan, with newer treatments such as endovenous thermal ablation and cyanoacrylate closure becoming more widely used. No RCT has directly compared the outcomes of these newer treatment methods with those of sclerotherapy. This warrants investigation in future studies.

4 | Chapter 4 Glossary of Terms and Concepts

4.1 | Abbreviations

APG, air plethysmography

CEAP, C (Clinical) E (Etiology) A (Anatomy) P (Pathophysiology)

CAC, cyanoacrylate closure

CVD, chronic venous disorders

CVI, chronic venous insufficiency (Synonym for CVD)

DVT, deep vein thrombosis

EHIT, endovenous heat-induced thrombosis

ETA, endovenous thermal ablation

EVLA, endovenous laser ablation

GSV, great saphenous vein

IPV, incompetent perforating vein

MDRPU, medical device related pressure ulcer

MRV, MR venography

NBCA, n-butyl-2-cyanoacrylate

NTNT, non-thermal non-tumescent treatment

PTE, pulmonary thromboembolism

PTS, postthrombotic syndrome (Synonym for sequelae of venous thrombosis)

RFA, radiofrequency ablation

SFJ, sapheno-femoral junction

SPJ, sapheno-popliteal junction

SSV, small saphenous vein

SVT, superficial venous thrombosis

TLA, tumescent local anesthesia

VCSS, venous clinical severity score

VLU, venous leg ulcers

VTE, venous thromboembolism

4.2 | Definitions of Terminology

4.2.1 | Lower Leg Ulcers

A collective term for all ulcers occurring in the lower leg caused by various factors. In Western countries, venous hypertension-related ulcers are the most common, accounting for approximately 70%–80% of lower leg ulcers. About 10% of lower leg ulcers are caused by arterial factors, while some involve both venous and arterial causes. Most lower leg ulcers are due to circulatory disturbances. Other causes include collagen diseases, vasculitis, pressure ulcers, malignant tumors, infections, and contact dermatitis.

4.2.2 | Venous Ulcers of the Lower Leg

Also referred to as venous stasis ulcers, stasis ulcers, or simply venous ulcers. These ulcers result from disturbances in venous return (venous stasis). Venous hypertension induces dermatitis, and minor trauma, such as a contusion, may trigger ulcer formation. These ulcers are frequently caused by primary or secondary varicose veins and often appear in the lower third of the leg or the dorsum of the foot.

4.2.3 | Stasis Dermatitis

Also known as stasis eczema. This is eczema or dermatitis caused by venous stasis or venous hypertension. It commonly occurs in the lower leg, frequently due to primary or secondary varicose veins.

4.2.4 | Venous Hypertension of the Leg

Also called venous hypertension. This condition involves high venous pressure in the lower leg, even during leg exercise in a standing position (e.g., tiptoeing or stepping exercises). During rest in a standing position, venous pressure corresponding to the central vein's height is exerted on the ankle, typically around 80–100 mmHg in a normal limb. However, leg exercise reduces this pressure to $\leq$ 30 mmHg due to the muscle pump's action. In primary varices, the pressure decreases only to about 60 mmHg due to venous valve insufficiency, and in conditions like deep vein thrombosis (DVT), pressure may show little reduction or even increase during exercise. This state, where peripheral venous pressure does not decrease during exercise, is referred to as venous hypertension of the leg.

4.2.5 | Varicose Veins

A condition where the superficial veins of the leg become dilated ($\geq$ 3 mm in the standing position) and tortuous. Although often referred to as "varices," some lesions may not be true varicose veins. In Japan, reticular and spider veins are also classified as varicose veins. However, according to the CEAP classification, reticular veins and telangiectasias are classified as class 1, while varicose veins are class 2. Varicose veins are categorized into primary and secondary types.

4.2.6 | Primary Varicose Veins

Also known as primary varices. These are caused by abnormalities within the dilated or tortuous superficial veins of the leg. Most varicose veins fall under this category.

4.2.7 | Secondary Varicose Veins

Also called secondary varices. These occur due to external factors rather than intrinsic abnormalities in the affected veins. Causes include pregnancy, intrapelvic tumors, arteriovenous fistulas, vascular tumors, DVT, and post-thrombotic syndrome

(PTS). Post-DVT varices are common, but diagnosis requires caution. When deep veins are reperfused after DVT, distinguishing secondary varices from primary varices can be challenging through patency examinations. In such cases, deep venous valve incompetence (valvular reflux) may impair the muscle pump function, leading to persistent venous hypertension. If the saphenous vein functions as a bypass for deep veins in the standing position, misdiagnosis as primary varices can occur, and surgical treatment may worsen venous hypertension and disease progression. Notably, a history of DVT does not always accompany clear valve reflux or deep vein occlusion.

4.2.8 | Leg Veins

Veins in the leg are classified into superficial veins, deep veins, and communicating branches (Figure 2).

4.2.9 | Superficial Veins of the Leg

These veins are located near the skin surface and include the great and small saphenous veins and their branches. Normally, approximately 10%–20% of the venous blood from the leg returns via these superficial veins. Both superficial and deep veins contain numerous valves, and venous return is facilitated by these valves and the muscle pump action. If deep veins are impaired due to DVT, superficial veins may act as bypasses and develop secondary varices if left untreated.

4.2.10 | Great Saphenous Vein

One of the superficial veins of the leg. It originates anterior to the medial condyle, ascends along the medial side of the lower leg, runs on the medial side of the knee and thigh, and drains into the femoral vein in the inguinal region. Before merging with the femoral vein, it receives numerous superficial veins, which are its branches, and also connects to deep veins through penetrating branches. The great saphenous vein typically consists of a single trunk but may split into two to three parallel vessels.

4.2.11 | Small Saphenous Vein

A single superficial vein, usually running along the posterior aspect of the leg. It originates posterior to the lateral condyle, ascends toward the popliteal region near the center of the posterior lower leg, and drains into the popliteal vein. Its upper third to half is located beneath the fascia. The small saphenous vein connects to deep veins through branches and to the great saphenous vein through superficial connections. Its course varies widely among individuals. In about 60%–70% of cases, it drains into the popliteal vein, but in some individuals,

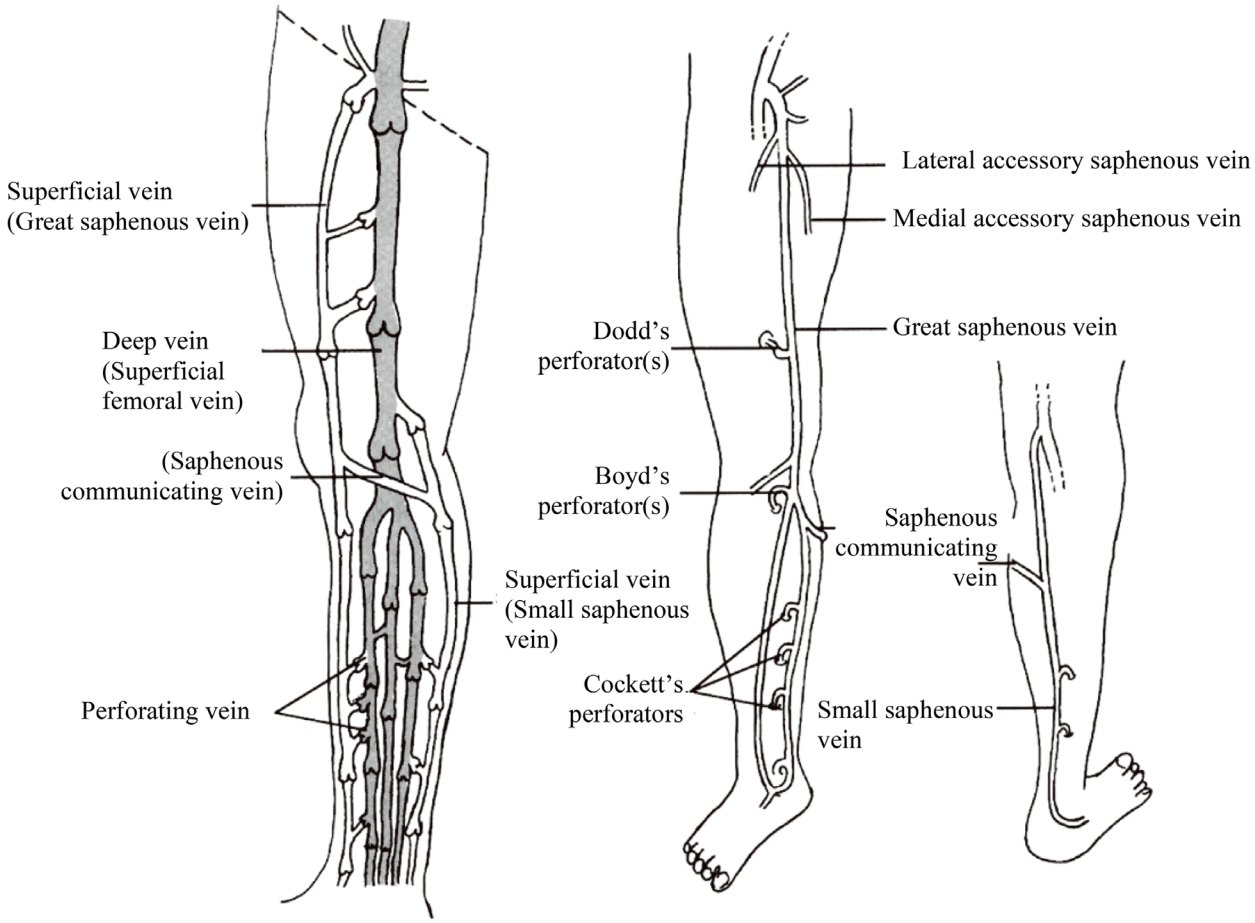


FIGURE 2 | Leg veins. Quoted and modified from Ito [70].

it bypasses the popliteal vein or continues ascending along the posterior thigh to join the great saphenous vein in the inguinal region.

4.2.12 | Deep Veins of the Leg

Veins that run parallel to arteries in the deep areas of the leg. Below the knee, veins named after their corresponding arteries merge to form the popliteal vein, which continues as the superficial femoral vein, joins the great saphenous vein in the inguinal region, and eventually drains into the external iliac vein. Deep veins are responsible for returning approximately 80%–90% of venous blood from the leg.

4.2.13 | Penetrating Branches

Veins with a diameter of 3 mm or less that connect superficial and deep veins. These veins contain venous valves, allowing blood to flow in a single direction from superficial to deep veins under normal conditions. They are also referred to as "perforators" or "perforating veins." In the guidelines issued by the Japanese Society of Phlebology, they are distinguished from communicating branches.

4.2.14 | Communicating Branches

Veins that connect superficial veins to one another. They are also known as "communicating veins."

4.2.15 | Insufficient Penetrating Branches

Penetrating branches that exhibit reflux from deep veins to superficial veins due to valve insufficiency associated with venous hypertension caused by leg varices.

4.2.16 | Clinical Classification of Primary Varices

Primary varices are classified into four types (1–4), although they may occur simultaneously (Figure 3).

Types (2–4) may be collectively referred to as small varices.

(1) Saphenous varices (Truncal Varices): This is the most common type of primary varices that require treatment. Great saphenous varices: caused by reflux in the great saphenous vein immediately below its junction with the femoral vein due to valve insufficiency. These varices appear as dilated and tortuous veins on the medial side of the thigh and lower leg. They may be accompanied by stasis dermatitis or ulcers above the medial condyle or the anterior lower leg.

Small saphenous varices: Result from valve insufficiency in the small saphenous vein below the sapheno-popliteal junction, causing dilation in the small saphenous vein or its branches on the posterior lower leg. These may be accompanied by stasis dermatitis or ulcers above the lateral condyle.

In advanced cases, reflux may extend to the great saphenous vein in the lower leg via intersaphenous veins, leading to varices

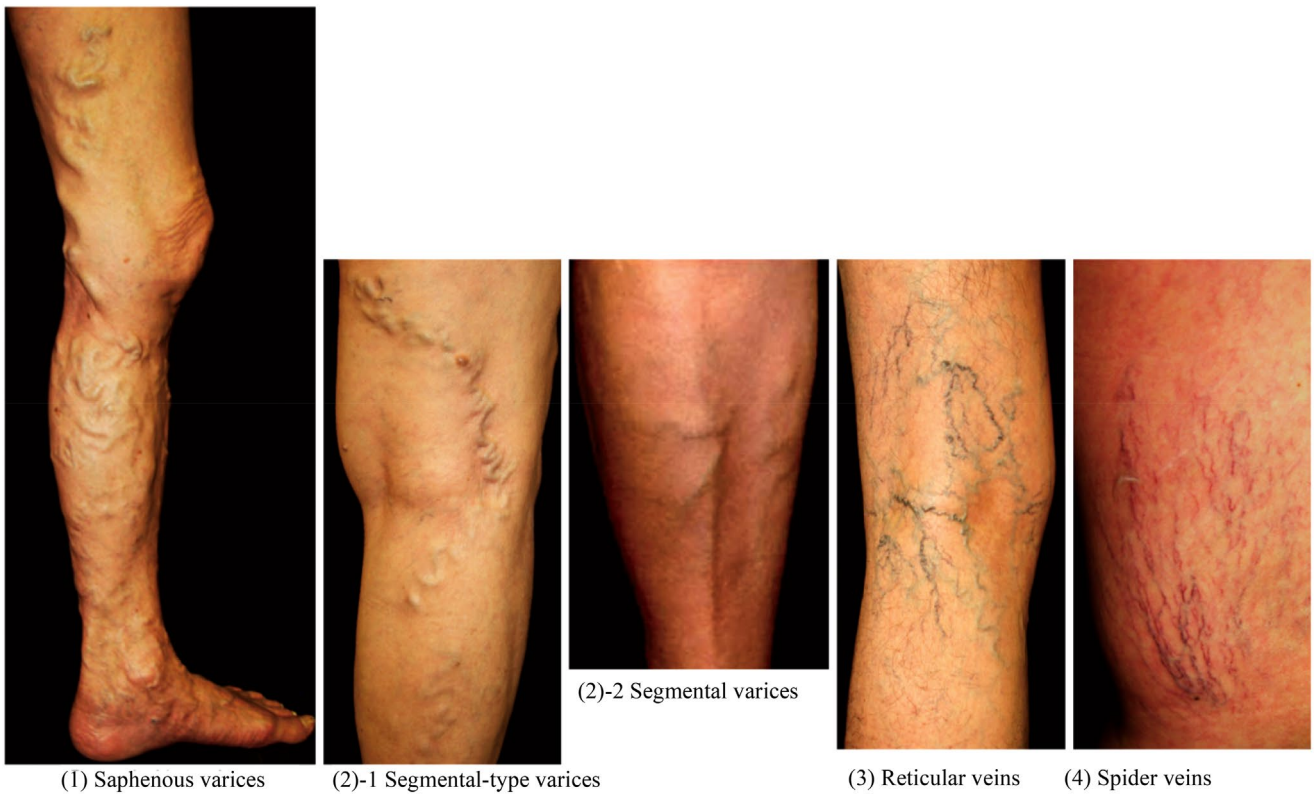


FIGURE 3 | Morphological classification of primary varicose veins. Quoted and modified from Ito [70].

on the medial side of the lower leg. A rash may also appear above the medial malleolus. When great and small saphenous varices coexist, circumferential venous stasis involving the lower half of the leg is sometimes observed.

(1) 1 Segmental-type varices: Typically not associated with valve insufficiency in the saphenous vein. These are considered varicose veins caused solely by valve insufficiency in branches. However, a clear definition is lacking.

(2) 2 Segmental varices: These refer to dilated superficial veins that drain into the saphenous vein. According to the terminology of the Japanese Society of Phlebology, these are also called branch varicose veins. However, since veins connected to the saphenous vein function as inflow veins rather than "branches" (as defined in arterial anatomy), they are more appropriately termed segmental varices.

(3) Reticular veins: Veins with a blue, retiform dilation measuring 2–3 mm in diameter.

(4) Spider veins: Thin, reddish purple veins, 1 mm or less in diameter, forming a cobweb-like pattern.

4.2.17 | Chronic Venous Insufficiency (CVI)

Also referred to as chronic venous disorders (CVD). This condition is defined as the occurrence of symptoms such as tiredness, edema, swelling, pain, secondary varices, eczema, skin sclerosis, and ulcers of the leg, resulting from impaired venous return to the heart due to various causes. It is caused by persistent venous hypertension of the leg, often due to untreated post-thrombotic syndrome (PTS) or varicose veins. Treatment should be guided by a definitive diagnosis based on the CEAP classification and an appropriate therapeutic strategy.

4.2.18 | Varicose Syndrome

Also known as stasis syndrome, though this term is primarily used in dermatology. Symptoms caused by venous stasis in the leg—such as edema, fatigue, stasis eczema, purpura, pigmentation, hemosiderin deposition, white atrophy of the foot and lower leg, and lower leg ulcers—are collectively referred to as varicose syndrome. Primary causes include untreated primary varicose veins and post-thrombotic syndrome (PTS). The treatment differs between these conditions: the former should be addressed with conservative management or surgery to treat the underlying varicose veins, while the latter requires strict compression therapy without surgical intervention. This syndrome is also referred to as CVI or CVD.

4.2.19 | CEAP Classification

The CEAP classification, developed by the American Venous Forum in 1994 and revised in 2020, is widely used to categorize varicose diseases of the leg. It classifies clinical signs (C) into 0–6, etiology (E) into c, p, s, and n, anatomical site (A) into s, d, p, and n, and pathophysiological dysfunction (P) into r, o, and n (Table 3).

4.2.20 | Deep Vein Thrombosis (DVT)

Primarily defined as the formation of thrombi in the deep veins of the leg. Pulmonary embolism (PE) often occurs alongside DVT, and together they may be referred to as venous thromboembolism (VTE) or venous thrombosis (VT). The etiology of thrombosis is described by Virchow's triad: (i) endothelial cell impairment, (ii) blood flow disturbance, and (iii) hypercoagulability. Recent studies suggest that DVT originates from thrombus formation in the soleal vein. Although the causes of DVT are diverse, it has been reported to occur in approximately half of patients following total knee replacement. While DVT and PE are sometimes called "economy class syndrome," this term is misleading, as these conditions can occur in contexts other than air travel.

4.2.21 | Central/Peripheral Deep Vein Thrombosis

DVT located central to the popliteal vein is referred to as central DVT, while DVT peripheral to the popliteal vein is called peripheral DVT. These are also known as proximal and distal types, respectively. DVT involving the three lower leg veins (anterior tibial vein, posterior tibial vein, and peroneal vein) and the intramuscular veins of the lower leg (sural vein and soleal vein) is classified as peripheral DVT.

4.2.22 | Guidelines for the Prevention of Deep Vein Thrombosis

The Guidelines for the Prevention of Pulmonary Thromboembolism/DVT (VTE) were first published in 2004. These guidelines were subsequently updated and integrated into the Guidelines for the Diagnosis, Treatment, and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (revision in 2017) (https://js-phlebology.jp/wp/wp-content/uploads/2020/08/JCS2017.pdf). As DVT is a significant cause of pulmonary embolism, frequently occurring after surgery or childbirth and often leading to severe outcomes, preventive measures and medications have been covered by insurance in Japan since 2004.

4.2.23 | Post-Thrombotic Syndrome

A condition primarily caused by venous hypertension in the leg during the chronic phase following DVT. During this phase, symptoms may improve due to the development of collateral blood flow and reperfusion of deep veins. However, if collateral development is inadequate or deep vein valve insufficiency (valvular reflux) persists, the leg's muscle pump fails to function properly, resulting in symptoms such as tiredness, edema, swelling, pain, secondary varices, eczema, pigmentation, dermal sclerosis, and leg ulcers due to sustained venous congestion.

TABLE 3 | CEAP classification, 2020.

Clinical classification (C class)	A_d Deep
C_0: No visible or palpable signs of venous disease	6. IVC Inferior vena cava
C_1: Telangiectasias or reticular veins	7. CIV Common iliac vein
C_2: Varicose veins	8. IIV Internal iliac vein
C_{2r}: Recurrent varicose veins	9. EIV External iliac vein
C3: Edema	10. PELV Pelvic veins
C_4: Changes in skin and subcutaneous tissue secondary to CVD	11. CFV Common femoral vein
C_{4a} : Pigmentation or eczema	12. DFV Deep femoral vein
C_{4b}: Lipodermatosclerosis or atrophie blanche	13. FV Femoral vein
C_{4c}: Corona phlebectatica	14. POPV Popliteal vein
C_5: Healed	15. TIBV Crural (tibial) vein
C_6: Active venous ulcer	15. PRV Peroneal vein
C_{6r}: Reccurent active venous ulcer	15. ATV Anterior tibial vein
	15. PTV Posterior tibial vein
	16. MUSV Muscular veins
s: symptomatic	16. GAV Gastrocnemius vein
a: asymptomatic	16. SOV Soleal vein
Etiological classification (E class)	A_p Perforator
E_p: Primary	17. TPV Thigh perforator vein
E_{3s}: Secondary	18. CPV Calf perforator vein
E_{si}: Secondary: intravenous	A_n No venous anatomic location identified
E_{se}: Secondary: extravenous	Pathophysiologic classification (P class)
E_s: Congenital	P_r: Reflux
E_n: No cause identified	P_o: Obstruction
Anatomic classification (E class)	$P_{r,o}$: Reflux and obstruction
A_s:Superficial	P_n: No pathophysiology identified
A_p:Perforator	
A_d:Deep	
A_n:No venous anatomic location identified	
A_s Superficial	
1. Tel Telangiectasia	
1. Ret Reticular veins	
2. GSVa Great saphenous vein above knee	
3. GSVb Great saphenous vein below knee	
4. SSV Small saphenous vein	
AASV Anterior accessory saphenous vein	
5. NSV Nonsaphenous vein	

Note: Modified from Akagi et al. [10].

4.2.24 | Thrombophlebitis

Inflammation of superficial veins primarily caused by thrombosis, distinct from DVT, which occurs in deep veins. Thrombophlebitis may complicate conditions such as Buerger's disease, Behçet's disease, coagulation or fibrinolytic abnormalities, thrombocytosis, and malignancies. In the legs, it often arises due to venous hypertension, while in the arms, it is frequently iatrogenic, caused by intravenous injections.

4.2.25 | Congenital Varices

Congenital varices are latent, inborn varices that frequently cause venous dilation from school age onward. Their symptoms resemble those of adult varices, but stripping surgery is often indicated if the deep veins are patent. A specific condition included in congenital varices is Klippel-Trenaunay syndrome, which is characterized by varicose veins, angiomas (including venous anomalies), and elongation of the affected limb.

4.3 | Explanations of Examinations

4.3.1 | Doppler Auscultation

An ultrasound-based examination used to evaluate blood flow (Figure 4). This test is essential for diagnosing peripheral arterial occlusive disease and leg vein disorders. The Doppler auscultator is small, lightweight, and easy to use, making it the most recommended tool for initial diagnosis. For leg vein examination, the procedure should be performed in the standing position, using a probe coated with a sufficient amount of gel to avoid compressing the skin. This test can detect blood flow in deep veins and reflux in superficial veins (e.g., great and small saphenous veins and their branches). Abnormalities are indicated by the presence of reflux murmurs when reflux is induced using the Valsalva maneuver or lower leg milking. Normally, no reflux murmur is heard in superficial veins.

FIGURE 4 | Doppler auscultator: Only an auscultator (left) and one with a blood flow direction-detecting function (right) are available.

4.3.2 | Trendelenburg Test

A traditional method for assessing valve function in the great and small saphenous veins and penetrating branches. The patient lies in a recumbent position with their legs elevated to empty the superficial veins and varices. If varices do not empty, this may indicate occluded deep veins or thrombi-filled varices. A tourniquet is applied to the femoral region while maintaining leg elevation, and the patient is asked to stand. Blood filling in varices is then observed. Rapid filling suggests insufficient communicating branches below the tourniquet or small saphenous vein reflux. If no swelling occurs, reflux in the great saphenous vein is likely prevented by the tourniquet. Swelling after tourniquet removal indicates great saphenous vein valve insufficiency.

4.3.3 | Perthes Test

A traditional test for evaluating deep vein patency and valve function in penetrating branches. The test begins by identifying varices in a standing patient, followed by the application of a tourniquet to the femoral region. The patient is asked to step or stand on tiptoes. If varices reduce in size due to muscle pump action, deep veins are likely patent. If no significant change is observed, insufficient communicating branches below the tourniquet are suspected. Worsening varices suggest deep vein obstruction.

4.3.4 | Leg Venography

An invasive X-ray examination primarily used to confirm deep vein patency. Performed in a semi-standing or standing position on a fluoroscopic table, the dorsalis pedis vein is punctured, and a contrast agent is injected. Fluoroscopy and radiography are used to observe the contrast agent's flow into deep veins. After confirming deep vein patency, the tourniquets are removed, and branches and varices are examined. The test is invasive and has a limited field of view.

4.3.5 | Contrast-Enhanced Computed Tomography of the Leg

This procedure involves injecting a contrast agent into an arm vein and acquiring CT images during the venous phase of the leg. The timing is adjusted to enhance vein imaging. The preparation of 3D images makes this technique useful for preoperative evaluation. Thrombi, if present, appear as filling defects.

4.3.6 | Color Doppler Ultrasonography of the Leg

This ultrasound method is used to examine the courses of veins, varices, and the locations of branches and penetrating branches. It provides detailed assessments of superficial veins, insufficient penetrating branches, and the condition of deep veins using duplex scanning.

4.3.7 | Duplex Ultrasonography

A method combining color Doppler imaging with conventional B-mode echography to visualize blood vessels, assess blood flow direction, velocity, and volume, and evaluate waveforms and color changes. It provides both morphological and functional insights.

4.3.8 | MR Venography (MRV)

A non-invasive imaging method for visualizing leg veins using magnetic resonance imaging (MRI). By emphasizing liquid signals in T2-weighted imaging and specifying blood flow direction, veins can be selectively visualized without arterial interference. This method provides detailed information about deep and superficial veins and their communicating branches. The preparation of 3D images makes MRV the most recommended preoperative evaluation method. However, clear images may not be obtained in cases of lower leg edema. MRV is contraindicated for patients with pacemakers or metallic foreign bodies in their bodies (Figure 5).

4.3.9 | Venous Plethysmography of the Lower Legs

A non-invasive test to evaluate the veins of the lower legs. This method assesses venous return function by measuring changes in lower leg volume associated with changes in body position, exercise, and avascularization. Variants include air plethysmography (APG), photoplethysmography (PPG), and strain gauge plethysmography, with APG being the most commonly used. Muscle pump plethysmography can evaluate or quantify the function of the lower leg muscle pump, while the compression method can assess the presence or absence of deep vein circulatory disturbances.

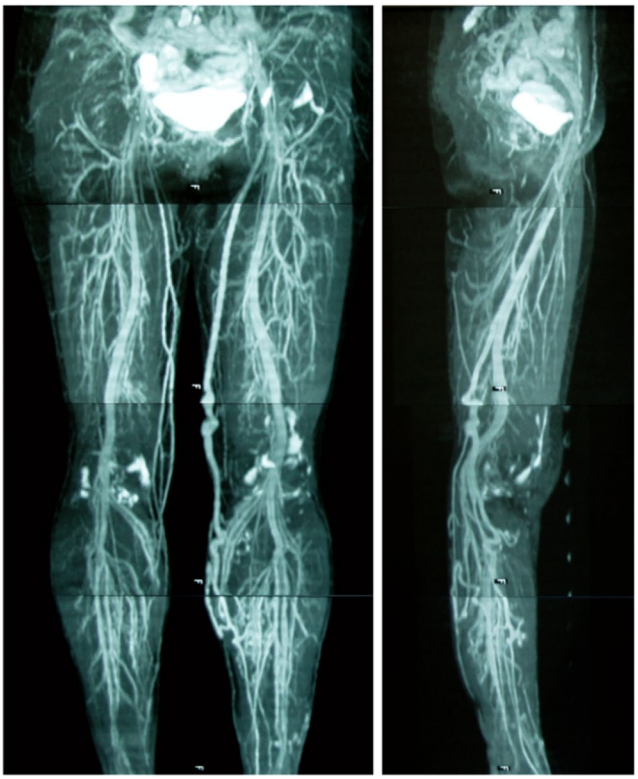


FIGURE 5 | MRV (left great saphenous varices), Right photograph: A lateral view of the left leg.

4.3.10 | Ankle Brachial Pressure Index (ABI or ABPI)

This test measures blood pressure in the arm and leg (typically in the posterior tibial and dorsalis pedis arteries) and calculates the ratio between the two. A normal ABI ranges from 1.0 to 1.4, with values of 0.9 or lower generally considered abnormal. However, arteriosclerosis of the leg can cause a falsely high ABI. Currently, this test can be performed quickly by simultaneously measuring arterial pressures and pulse wave velocity, facilitating the differentiation between normal circulation and arteriosclerosis.

4.4 | Explanation of Treatments

4.4.1 | Compression Therapy

This is the most essential conservative treatment for varicose veins, DVT, and lymphedema. Elastic bandages or stockings are used, with elastic bandages preferred for patients with ulcers due to their adjustable compression pressure. For patients without ulcers, stockings are more convenient. Special caution is necessary for patients with peripheral artery disease (PAD), as compression therapy may be contraindicated when the ABI is <0.8. In cases requiring stronger compression pressure for ulcers, double-wrapping with slightly elastic bandages can be effective. Compression garments should be applied immediately upon waking in the morning and worn until bedtime. During sleep, the lower legs should be elevated approximately 10 cm, for example, by placing two cushions under the legs. Compression therapy should be continued for untreated varices and for 2–3 months after surgical treatment.

4.4.2 | Venous Compression Treatment

Since 2020, venous compression treatment for chronic venous insufficiency (J001-10) has been covered by health insurance in Japan. It is calculated as a wound treatment fee but requires physicians and nurses to complete training on elastic stocking/compression therapy, provided by the Japanese Society of Phlebology. Facilities must meet certification criteria to calculate medical fee points. This treatment can be claimed once a month for up to 3 months (or 6 months if the initial ulcer size exceeds 100 cm^2), provided the patient meets the necessary conditions for chronic venous insufficiency-related refractory ulcers.

For more details, visit the Japanese Society of Phlebology website:

https://js-phlebology.jp/?page_id=4344.

4.4.3 | Reimbursement for Medical Supplies

Since 2020, the cost of medical supplies, such as elastic garments, for treating chronic venous insufficiency-associated refractory ulcers, is reimbursable. Patients can purchase elastic stockings following instructions provided by their attending physicians and apply for medical expense benefits by submitting the required documents to the Employees' Health Insurance Division (for National Health Insurance and Livelihood Protection System) or the National Health Insurance Association (for social insurance).

Further details can be found in the notices from the Ministry of Health, Labour, and Welfare:

https://www.mhlw.go.jp/bunya/iryouhoken/iryouhoken13/dl/200327_04.pdf.

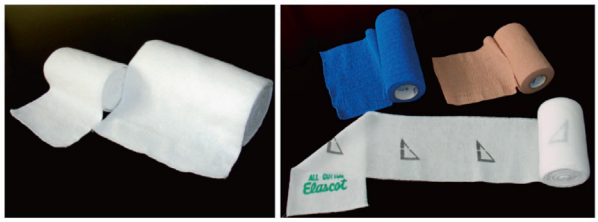


FIGURE 6 | Elastic bandages. Left: Suportex (10 cm and 15 cm in width), Right: Cohesive elastic bandage (upper), Elascot-Tension Guide (lower).

https://www.mhlw.go.jp/bunya/iryouhoken/iryouhoken13/dl/200327_05.pdf.

4.4.4 | Elastic Bandages

Stretchable bandages used in compression therapy. They are relatively inexpensive and allow for adjustments in compression force and coverage area. However, they are prone to displacement or loosening, and the compression force may vary depending on how they are applied. To address these issues, cohesive elastic bandages, which adhere upon application, and elastic bandages with guides for applying uniform compression pressure are also available (Figure 6). In cases with ulcers, elastic bandages are easier to use than stockings, as they cause less pain from compression and are less likely to displace gauze covering the ulcers. When bandaging, the foot should also be compressed. For lower leg compression, bandages with a width of 10 cm are recommended, while bandages measuring 15 cm in width should be used for full-leg compression (Figure 7). Achieving uniform compression requires experience and proper technique by the therapist.

4.4.5 | Elastic Stockings/Socks

Stockings used for the treatment of leg vein disorders and lymphedema. They are also employed to prevent intra- or postoperative DVT. Various types are available, including pantyhose, stockings, and knee sock styles, with or without

FIGURE 7 | How to apply elastic bandages (10 cm width). Modified from Ito et al. [1].

a toe section. Products from several manufacturers are marketed with size options (SS, S, M, L, and LL) and compression levels (strong, medium, mild), allowing selection based on the leg's length and thickness (Table 4). Thicker stockings are more suitable for treating lymphedema.

Patients must receive sufficient guidance when using stockings for compression therapy. It should be explained that stockings of the correct size are inherently difficult to put on, while those that are easy to wear are likely unsuitable and provide insufficient compression. Rubber gloves, such as those used in the kitchen, can help make the process easier (Figure 8). Additionally, supportive devices for donning elastic stockings are available on the market (Figure 9).

4.4.6 | Support Stockings/Socks

Elastic stockings marketed under names like "tightening stockings" or "compression stockings" as articles of clothing. Since putting on medical-grade stockings requires significant grasping strength, elderly patients or those with reduced grip strength may be advised to wear support stockings in multiple layers.

4.4.7 | Surgery for Varicose Veins

A comprehensive term for surgical treatments for primary varicose veins. Procedures such as stripping, high ligation, sclerotherapy, endovenous thermal ablation, subfascial endoscopic perforator vein surgery, and endovascular embolization are covered by health insurance. Regardless of the method chosen, surgery must follow confirmation of deep vein patency, marking vein locations using Doppler auscultation and echography in standing and recumbent positions, and determination of the surgical site. Details of each procedure are described below.

4.4.8 | Stripping of Varices

Also known as venous stripping, this surgical technique has been used for over 100 years. With the widespread adoption of endovascular treatments, stripping is now reserved for cases involving severe dilation or marked tortuosity of the saphenous vein. In this procedure, the incompetent saphenous vein is removed, and insufficient communicating branches are blocked, yielding stable outcomes. To prevent postoperative venous thrombosis, early ankle movement or walking is encouraged, and tumescent local anesthesia (TLA) is increasingly employed. After high ligation and separation of the great saphenous vein in the inguinal region, a stripping wire is inserted from the lower leg toward the inguinal region. The vein is then stripped using either a Babcock stripping method (with a head/olive) or an invagination stripping technique (without an olive). While the latter causes less nerve damage, there is a risk of vein rupture during stripping. Recurrence rates of 30%–40% have been reported within 5 years due to reflux in other superficial veins.

4.4.9 | High Ligation

This method is suitable for moderate saphenous vein dilation and is performed under local anesthesia. For great saphenous varices, a skin incision is made near the inguinal crease, and for small saphenous varices, in the popliteal region. The saphenous vein is exposed, its junction with the deep vein is identified, and it is ligated and separated without causing stenosis. Recurrence is sometimes observed, and the introduction of endovascular treatment has reduced the frequency of this method.

4.4.10 | Sclerotherapy

A technique involving the direct infusion of a sclerosing agent into small varices. Polidocanol (Polidocasclerol) is covered by health insurance. A thin needle (25 G or 27 G) is used to inject 0.5%–3% polidocanol, and the site is compressed with an elastic bandage (compression sclerotherapy). Foam sclerotherapy, where polidocanol is mixed with air or carbon dioxide to form foam, has become the preferred method.

4.4.11 | Foam Sclerotherapy

This is a type of sclerotherapy in which a foamy sclerosing agent is prepared using 0.5%–3% polidocanol (Polidocasclerol) and infused into the vein. The foam is created using two disposable syringes and a three-way stopcock. The syringes are firmly connected to the stopcock at right angles, and the sclerosing agent is mixed with air or carbon dioxide by alternately pushing the syringes (approximately 20 times within 10 s) to form the foam. According to the package insert, foam sclerotherapy should be performed using 2 mL of 1% Polidocasclerol injection or 2 mL of 3% Polidocasclerol injection when treating the trunk of saphenous varices. However, the efficacy and safety of this agent have not been established for primary varices larger than 12 mm in diameter when using foam sclerotherapy.

4.4.12 | Tumescent Local Anesthesia (TLA)

TLA was introduced by Klein et al. as an anesthetic technique for liposuction (*J Dermatol Surg Oncol* 1990;16:248–263). It is now widely used for varicose vein surgeries. The technique involves using a low-concentration local anesthetic (0.05%–0.1% lidocaine with adrenaline). Due to adrenaline's suppression of lidocaine absorption, doses exceeding the usual maximum limit of lidocaine can be safely used. Typically, adrenaline-containing lidocaine (Xylocaine injection 1% with Epinephrine (1:100 000)) is diluted with physiological saline to prepare a 0.1% solution for use in the procedure.

4.4.13 | Endovenous Thermal Ablation (ETA)

ETA is a minimally invasive procedure that is as effective as saphenous vein stripping for treating varicose veins. This treatment involves cauterizing varices using a catheter. Both endovenous laser ablation (wavelengths 980 nm and 1470 nm) and radiofrequency ablation are covered by health insurance (Figure 10). During the procedure, the saphenous vein is punctured under ultrasound guidance, and TLA is administered around the vein to be cauterized. The catheter tip (laser fiber or radiofrequency device) is placed just distal to

TABLE 4 | Representative elastic stockings.

	Elastic stockings for varicose veins				
Classification	**≤20 mmHg (27 hPa)**	**20–30 mmHg (27–40 hPa)**	**30–40 mmHg (40–53 hPa)**	**≥40 mmHg (53 hPa)**	**Elastic bandages • tubes**
Company name					
ALCARE	Ansilk-1 Calf Stockings, Panty Hose, and Maternity (all: toe stockings) Size: S, M, L Vivanurse Calf Stockings Ankle pressure: 19 hPa	Ansilk-2 Calf Stockings (toe/open toe stockings), Stockings, Panty Hose, and Maternity (toe stockings) Size: SS, S, M, L, LL Ansilk-2 Bright	Ansilk-3 Calf Stockings (open toe stockings). Stockings (open toe stockings) Size: SS, S, M, L, LL		Suportex, Elascot, Elascot-Tension Guide
SIGMAX	Thigh-length, knee-length CV slight stockings, knee-length socks Size: S, M, L	Thigh-length, knee-length CV normal stockings, knee-length socks Size: S, M, L	Thigh-length, knee-length CV strong stockings, knee-length socks Size: S, M, L		
JMS		Leg science "Mai" knee-high socks (toe/open toe), stockings (toe/open toe) Size: S, M, L, LL			
SOLVE	Therafirm, slightly weak compression pressure 10–15 mmHg (13–20 hPa) Therafirm, slightly strong compression pressure 15–20 mmHg (20–27 hPa) Knee-high socks, stockings, pantyhose, VENOFLEX cotton knee-high socks 15–20 mmHg for males/females Size: S, M, L, XL	Therafirm, strong compression pressure 20–30 mmHg (27–40 hPa) VENOFLEX cotton knee-high socks 20–36 mmHg for males/females Size: S, M, L, LL, or XL			

(Continues)

TABLE 4 | (Continued)

Classification	Elastic stockings for varicose veins				Elastic bandages • tubes
	≤20 mmHg (27 hPa)	20–30 mmHg (27–40 hPa)	30–40 mmHg (40–53 hPa)	≥40 mmHg (53 hPa)	
TERUMO	Ruruho 19 JOBST UltraSheer 20, Light Wear, For Men Ambition 20	Ruruho 33 JOBST UltraSheer 30, Power Support Stockings, For Men Ambition 30	For Men Ambition 40	Ulcer Care	
Toray Medical Co. Ltd	COCOFY	COCOFY PLUS	COCOFY PLUS	—	
NAK CORPORATION	Mediven plus class 1 VENOSAN VENOSAN 4000 knee-high socks, stockings, pantyhose Size: XS, S, M, L, XL	Mediven plus class 2 VENOSAN 5000 knee-high socks, stockings, pantyhose Size: S, M, L, XL	Mediven plus class 3 VENOSAN 7000 knee-high socks, stockings, pantyhose Size: XS, S, M, L, XL	VENOSAN 3000 knee-high socks, stockings, pantyhose Size: S, M, L, XL	Tg grip elastic, cotton cylindrical bandage (A: width, 4.6 cm–M: width, 37.5 cm)
LimFix	RxFit thin, weak pressure, breathable, appropriate in the summer Size: S, M, L, LL RxFit cotton, weak pressure, cotton blend material, weak pressure RxFit 5 5-toe type Tapipo (18–24 mmHg) Pile-like towel fabric Size: S, M, L RxFit microfiber, weak pressure quick-drying, absorbent Size: XS, S, M, L	RxFit thin, medium pressure, breathable RxFit for men, large-size rib knit Size: S, M, L RxFit microfiber, medium pressure, quick-drying, absorbent Size: XS, S, M, L	RxFit thick, medium pressure, for cases in which sufficient compression is necessary Size: S, M, L, LL	RxFit, strong pressure (45 mmHg) Size: S, M, L, LL	

FIGURE 8 | Elastic stockings. Pantyhose (upper left), thigh-high stockings (upper right), knee-high socks (lower left), and rubber gloves for persons with a weak grip strength (lower right).

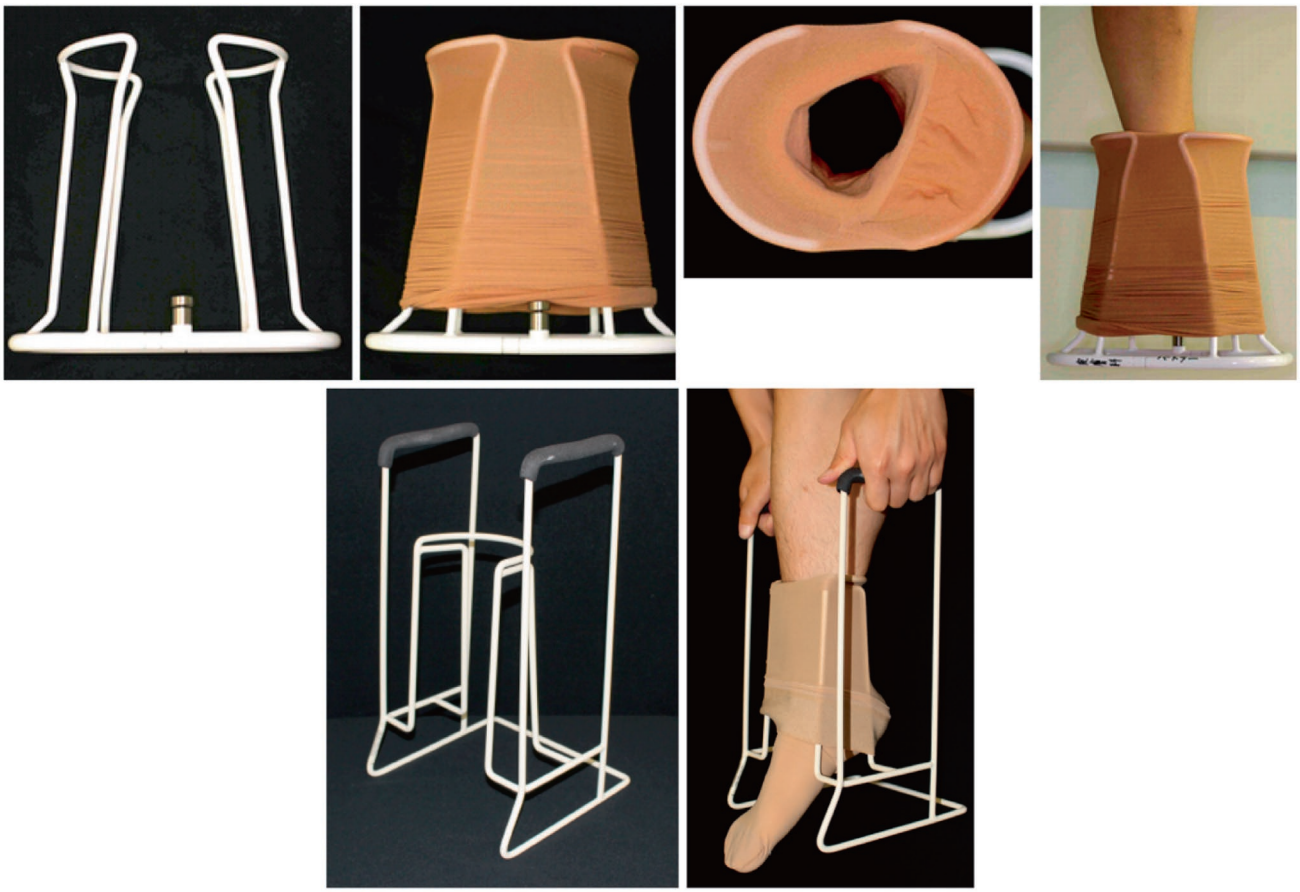


FIGURE 9 | Elastic stocking application aid devices. Butler: upper, Stocking Donner: lower. Other application aid devices include the Doff N' Donner and Easy-Slide for open toe stockings.

the saphenous-deep vein junction under ultrasound guidance. The vein is then cauterized while its position is confirmed via echography. This process is repeated as the device is gradually withdrawn to achieve complete ablation or occlusion of the vein. ETA is not suitable for veins that are markedly tortuous or have a large diameter. After the procedure, thrombus formation around the saphenous-deep vein junction (endovenous heat-induced thrombus, EHIT) can occur, potentially leading to DVT. Therefore, follow-up with multiple echographic evaluations is required. Additionally, this procedure can only be performed under insurance coverage by physicians who have completed the necessary training. Indications and exclusion criteria for ETA are listed in Table 5.

4.4.14 | Subfascial Endoscopic Perforator Vein Surgery (SEPS)

This technique is indicated for patients in whom the effects of varicose vein surgery are expected to be insufficient. It is

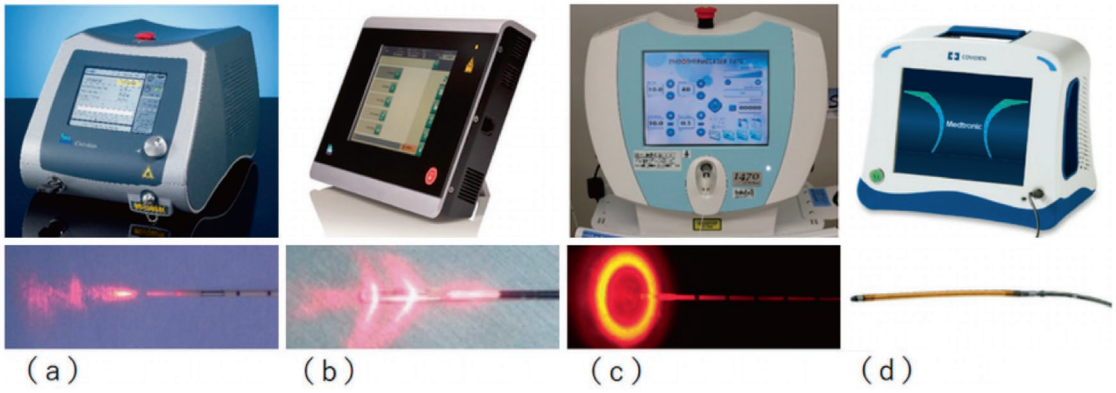


FIGURE 10 | Endovenous thermal ablation devices covered by health insurance in Japan. (a) ELVeS laser: 980 nm bare-tip fiber, (b) ELVeS laser 1470: 1470 nm radial 2-ring fiber, (c) LSO1470 laser: 1470 nm radial 1-ring fiber, (d) Radiofrequency (high-frequency generator) ClosureRFG Generator, ClosureFAST catheter. (a, b: Integral Corporation, c: MEDICO'S HIRATA INC, d: Covidien Japan Co. Ltd). Modified from the Clinical Practice Guidelines for Endovenous Thermal Ablation for Varicose Veins 2019 supervised by the Japanese Society of Phlebology.

TABLE 5 | Indication and exclusion criteria for endovenous thermal ablation.

"Indication and exclusion criteria" described in the guidelines for endovascular treatment for varicose veins
1. Indication criteria
① Deep veins are patent
② The mean diameter of saphenous veins 5 to 10 cm distal to the sapheno-femoral junction (SFJ) or sapheno-popliteal junction (SPJ) is ≥ 4 mm. Furthermore, a mean diameter of ≤ 10 mm is recommended
③ Symptoms of varicose veins (fatigue, pain, edema, cramps) are present, or stasis dermatitis is present
④ Even in the presence of saphenous venous valve insufficiency, endovascular treatment is not indicated when the terminal valve is normal in the absence of valve insufficiency at the SFJ. However, cases in which Dodd's perforator is the source of reflux are excluded
2. Exclusion criteria: Exclusion criteria for endovascular treatment are shown below:
① Clinical class C1 (spider or reticular veins) in the CEAP classification
② Patients with DVT or a history of DVT
③ Those with disturbance of arterial blood flow
④ Those with difficulties in walking
⑤ Those with multiple organ disorder or DIC
⑥ Those taking oral contraceptives or hormonal agents
⑦ Those with serious heart disease
⑧ Those with shock or in a pre-shock state
⑨ Pregnant women or patients who may be pregnant
⑩ Patients receiving steroid therapy
⑪ Those with Behcet's disease
⑫ Those taking drugs for osteoporosis (raloxifene) or multiple myeloma (thalidomide)
⑬ Those with thrombotic predispositions (protein C deficiency, protein S deficiency, antithrombin III deficiency, antiphospholipid antibody syndrome).

Note: Extracted from the *Japanese Journal of Phlebology* [71].

particularly applicable to those with extensive lower leg skin involvement, such as pigmentation, sclerosis, atrophy, or ulcers, where an incompetent perforator vein has been identified via echography, and reflux has been confirmed. SEPS replaces the older open perforator vein surgery, known as Linton surgery. The procedure involves inserting an endoscope through an area

above the incompetent perforator vein site to perform subfascial ablation or separation of the vein.

4.4.15 | Endovascular Embolization

Endovenous thermal ablation (ETA) involves the use of heat for vein ablation or closure and requires tumescent local anesthesia (TLA). However, complications such as pain and subcutaneous hemorrhage during TLA have been reported. In Europe and the United States, a more minimally invasive alternative, known as non-thermal non-tumescent (NTNT) treatment, has been developed. NTNT treatments do not involve thermal ablation or TLA. One representative NTNT method is endovascular treatment using a cyanoacrylate (CA) adhesive, termed cyanoacrylate closure (CAC) or glue therapy. In 2015, the VenaSeal Closure System (Medtronic, Minneapolis, USA) became the first CAC treatment to receive approval from the Food and Drug Administration (FDA). In Japan, the same product was approved and covered by health insurance as the VenaSeal Closure System (VenaSeal) in 2019 (Figure 11).

5 | Chapter 5 Guide for the Management of Lower Leg Ulcers/Varicose Veins

5.1 | Diagnosis of Lower Leg Ulcers/Varicose Veins

5.1.1 | Lower Leg Ulcers Are Primarily Associated With Disturbances in Venous Return (Venous Hypertension of the Leg)

- Regarding the etiology of lower leg ulcers, there is one analytical epidemiological study [72] and expert opinions [73–75]. In the United States, approximately 600 000 new cases of lower leg ulcers occur annually, with venous return disturbances implicated in around 80% of cases [72, 73]. A report from Germany similarly indicated that 80%–90% of lower leg ulcers are associated with vascular damage [74].
- In Japan, a 2018 survey on venous diseases conducted by the Japanese Society of Phlebology reported that among 587 legs (513 patients) with venous ulcers, 497 (84.7%) were associated with primary varicose veins, indicating a significantly high incidence [76]. It is crucial to assess venous ulcers of the lower leg linked to primary or secondary varicose veins as significant etiological factors for lower leg ulcers [75, 77, 78]
- When diagnosing a lower leg ulcer, venous ulcers should be strongly suspected. Other potential causes include congenital vascular dysplasia, such as Klippel–Trenaunay syndrome and Parkes–Weber syndrome [76]. Studies have also shown that vascular diseases are not involved in approximately 10% of lower leg ulcers [72–74]. Therefore, clarifying the etiology is essential.

FIGURE 11 | VenaSeal closure system (VenaSeal). https://www.medtronic.com/jp-ja/healthcare-professionals/products/cardiovascular/Superficial_Vein/venaseal.html.

5.1.2 | Venous Ulcers of the Lower Leg Cause Characteristic Symptoms, and an Inquiry Is Also Important

- Before ulcer formation, symptoms such as lower leg swelling, fatigue, and pruritus related to primary varicose veins or DVT often occur from morning to evening. Many patients report experiencing cramps during nighttime sleep. In those with primary varicose veins, a history of standing work or leg-intensive sports is common. For patients with DVT, it is important to investigate the presence of coagulopathies, prolonged bed rest, history of malignant tumors, trauma or leg fixation, and prior surgeries, particularly total knee or hip arthroplasty [75, 78].

5.1.3 | Patients Should Be Examined in the Standing Position for the Diagnosis of Varicose Veins

- Varicose veins can be identified through visual inspection and palpation of dilated, curved, or tortuous superficial veins in the standing position. These abnormalities may not be visible in the supine position and can even be missed in a sitting position. Diagnosis may also be difficult in the standing position if the femoral region is compressed by tight clothing. Ultrasonography should always be performed in the standing position for accurate diagnosis.

5.1.4 | Doppler Auscultation or Duplex Ultrasonography Should Be Used for Detailed Evaluation of Venous Leg Ulcers

- Doppler auscultation is widely utilized as a simple, noninvasive diagnostic tool [42–44, 79–81].
- This method aids in diagnosing varicose veins or superficial venous valve insufficiency and, in some cases, allows for an accurate diagnosis of venous insufficiency without the need for ultrasonography. A study reported that the sensitivity and specificity of Doppler auscultation are comparable to those of ultrasonography [44]. However, evaluating deep veins and obtaining morphological information are challenging with this method.
- Duplex ultrasonography provides a detailed morphological assessment of superficial venous blood flow and enables

both functional and morphological diagnoses of superficial, deep veins, and perforators. Its advantages include being noninvasive, cost-effective, and capable of real-time observation [45, 46].

5.2 | Evaluation of Varicose Veins

5.2.1 | Chronic Venous Insufficiency (CVI) Should Be Classified Using the CEAP Classification by Performing Ultrasonography

- CVI refers to a condition characterized by chronic symptoms or signs caused by morphological or functional abnormalities of the venous system. The term "chronic venous disease" (CVD) has also been proposed [82]. While these terms are often used interchangeably, CVD was originally a morphological classification system introduced by Widmer et al. in 1978 [83]. Thereafter, it was revised, and the CEAP classification was reported as a systematic classification system of CVD in 1995 [84], with a subsequent revision published in 2020 [85]. The CEAP classification categorizes clinical signs (C: Clinical) into six classes (0–6), etiology (E: Etiological) into p (primary), s (secondary), c (congenital), and n (no venous disease), anatomical distribution (A: Anatomical) into s (superficial veins), d (deep veins), p (perforator veins), and n (no venous location identified), and pathophysiology (P: Pathophysiological) into r (reflux), o (obstruction), and n (no venous abnormality). This classification allows for the selection of appropriate treatment strategies (Table 3 in Chapter 4).

5.2.2 | Venous-Phase Contrast-Enhanced CT and MR Venography (MRV) are Recommended

- Previously, leg venography was the gold standard for diagnosing acute DVT [86]; however, its use has decreased due to its invasiveness and complexity. Instead, meta-analyses have shown the utility of other imaging methods, such as ultrasonography, venous-phase contrast-enhanced CT, and MRV [14, 15, 87, 88]. One study reported that the diagnostic sensitivity and specificity of ultrasonography for central and peripheral DVT were 94.2% and 93.8%, respectively, compared with leg venography [14]. Another study found that MRV achieved a sensitivity of 91.5% and specificity of 94.8%, although various imaging methods of MRV exist [87]. Additionally, contrast-enhanced CT demonstrated a sensitivity of 95.9% and specificity of 95.2% compared to ultrasonography [88]. These studies indicate that ultrasonography, MRV, and contrast-enhanced CT provide diagnostic results similar to those of venography for confirming DVT and assessing deep vein patency [14, 87, 88].
- Furthermore, air plethysmography (APG), a physiological function test for leg veins, offers noninvasive assessment of venous kinetics. It is useful for evaluating preoperative venous return status, determining postoperative improvement, and diagnosing recurrence through serial monitoring.
- Despite advancements in imaging techniques, diagnosing chronic DVT remains difficult [38, 39]. Careful interpretation of imaging results is required to ensure an accurate diagnosis.

5.3 | Conservative Treatment for Venous Leg Ulcers Associated With Primary or Secondary Varicose Veins

5.3.1 | Compression Therapy Is Necessary for Primary Varicose Veins or Post-Thrombotic Syndrome (PTS)-Related Secondary Varicose Veins, Excluding Acute DVT

- For symptomatic varicose veins, compression therapy is an essential basic treatment. Surgical intervention may also be considered for primary varicose veins associated with valve insufficiency.
- Varicose veins are categorized into primary and secondary types. Primary varicose veins result from reflux of venous blood into the lower leg due to superficial venous valve insufficiency, leading to venous hypertension. Secondary varicose veins often occur as a result of PTS.
- PTS-related venous ulcers of the lower leg are particularly challenging to treat. However, strict compression therapy can improve mild to moderate cases [56]. Continuous compression therapy for DVT in the post-acute phase significantly reduces the incidence of PTS [57].
- The mechanisms of compression therapy include enhancing muscle pump action through repulsive forces between the muscle and compression, reducing venous diameter and increasing venous flow velocity, decreasing venous reflux, improving edema and microcirculation by reducing leakage and enhancing reabsorption, and reducing inflammatory cytokines in peripheral cells [55]. These mechanisms contribute to improvements in venous leg ulcers.
- Venous leg ulcers are associated with venous hypertension in areas adjacent to the ulcer, resulting from venous insufficiency. Healing may be achieved by reducing this hypertension. Initial treatment involves compression therapy using elastic bandages or stockings. The ulcer site should be disinfected, and a non-adhesive gauze dressing applied before compression. Primary etiological factors for varicose veins include valve insufficiency in the saphenous vein and venous reflux through incompetent perforating veins. In secondary varicose veins, venous hypertension caused by deep vein insufficiency or valve failure delays wound healing, making venous leg ulcers more refractory.

5.3.2 | For Compression Therapy, Elastic Stockings Are Usually Used, but Elastic Bandages Are Used When Patients With Venous Leg Ulcers or Elderly Patients Are Unable to Wear Elastic Stockings

- The compression pressure of elastic stockings (at the ankle) is classified into mild (< 20 mmHg), weak (20 to 29 mmHg), middle (30 to 39 mmHg), and strong (≥ 40 mmHg) pressures. As a guide for selection, a mild compression pressure

is indicated for the prevention of DVT and management of disuse edema, a weak pressure for varicose veins without dermal symptoms and disuse edema, a middle pressure for varicose veins with dermal symptoms, PTS, and congenital vascular anomalies, and a strong pressure for severe PTS and lymphedema. After surgery for varicose veins, weak to middle pressures are appropriate. As there are several sizes of elastic stockings, it is necessary to select an adequate size of the product by measuring ankle and calf circumferences.

- Elastic bandages are initially applied to the dorsum of the foot, overlapping by half the width of the bandage in a spiral pattern. The bandage should be wrapped from the periphery toward the center with consistent tension. Some bandages include pressure indicators for uniform application. For ulcer cases, the ulcer site may be bandaged first. Complications such as peroneal nerve palsy, medical device-related pressure ulcers (MDRPU), arterial blood flow disturbances, and contact dermatitis must be considered during compression therapy.
- Educating patients about the necessity of compression therapy and proper application methods is crucial, often in collaboration with nurses. Special attention should be given to the potential development of peripheral artery disease (PAD), particularly in elderly patients. Patients should also receive lifestyle guidance, including avoiding prolonged standing or sitting, performing leg exercises or walking to activate the lower leg muscle pump, and following a weight management plan if obese.
- In some elderly patients, maintaining compression therapy may be difficult due to challenges such as limited finger strength for donning stockings, pressure pain at the ulcer site, or discomfort caused by shear stress despite protective gauze. These difficulties can make consistent compression therapy challenging.
- Compression therapy aims to mitigate venous hypertension. During sleep in the supine position, venous pressure at the ulcer site decreases to levels similar to central venous pressure, allowing compression to be relaxed. Patients must understand that "compression therapy is essential for treating this ulcer." Without compression therapy, local ulcer treatment alone may not be effective.

5.4 | Surgical Treatment for Lower Leg Ulcers Associated With Primary Varicose Veins

The site of reflux in leg veins of patients with primary varicose veins is classified into superficial veins (e.g., the great and small saphenous veins), deep veins (e.g., the femoral and popliteal veins), and perforators connecting deep to superficial veins. Treatment for primary varicose veins typically targets reflux in the saphenous vein. Surgical options include stripping, high ligation, endovenous thermal ablation (laser or radiofrequency), and cyanoacrylate closure.

This section explains the significance of combining surgical treatments with compression therapy and local treatment for lower leg ulcers associated with primary varicose veins.

5.4.1 | Stripping/High Ligation Significantly Decreases the Recurrence Rate of Venous Leg Ulcers. There Was no Significant Difference in the Healing Rate of Venous Leg Ulcers, but a Decrease in the Recurrence Rate of Venous Leg Ulcers May Contribute to Long-Term Effects

- Three RCTs compared combined surgical and compression therapy with compression therapy alone [60–62].
- Gohel et al. [60]: This study compared 500 patients (500 legs) and found no significant difference in the ulcer healing rate 3 years post-treatment (89% in the compression group vs. 93% in the surgical group, $p = 0.73$). However, the ulcer recurrence rate 4 years after treatment was significantly lower in the surgical group (51% vs. 27%, $p < 0.01$).
- Zamboni et al. [61]: This study involving 45 patients (47 legs) reported a significantly higher ulcer healing rate in the surgical group 3 years post-treatment (100% vs. 96%, $p < 0.02$) and a lower ulcer recurrence rate (9% vs. 38%, $p < 0.05$).
- Gent et al. [62]: In 170 patients (200 legs), no significant difference was observed in ulcer healing rates 3 years post-treatment (83% in the compression group vs. 73% in the surgical group, $p = 0.24$) or recurrence rates (22% vs. 23%, $p < 0.01$).
- There was no significant difference in the healing rate of venous leg ulcers. However, stripping or high ligation improves hemodynamics, such as reflux of deep veins or incompetent perforating veins, through resection of superficial veins [89]. These procedures significantly reduce the ulcer recurrence rate. Therefore, they may be effective from the long-term perspective of shortening the duration of venous leg ulcers.

5.4.2 | Endovenous Thermal Ablation Significantly Improves the Healing Rate of Venous Leg Ulcers

- Endovenous thermal ablation significantly improves ulcer healing rates. Two RCTs compared combined ETA and compression therapy with compression therapy alone [63, 64].
- Puggina et al. [63]: Among 56 patients, the ulcer healing rate was significantly faster in the ETA group ($0.739 \pm 0.498\,cm^2$/week vs. $0.495 \pm 0.409\,cm^2$/week in the compression group, $p = 0.049$). Additionally, the ulcer recurrence rate at 12 months was significantly lower in the ETA group (HR 0.083, 95% CI [0.011–0.0632], $p < 0.001$). However, long-term follow-up data are limited.
- Gohel et al. [64]: Among 450 patients with venous ulcers, the ETA group demonstrated a significantly higher healing rate (RR 1.38, 95% CI [1.13–1.68], $p = 0.001$).

5.4.3 | Cyanoacrylate Closure has Been Established as a Treatment for Primary Varicose Veins. However, No Study has Examined the Healing Rate of Venous Leg Ulcers; Therefore, a Prospective Study Should Be Performed in the Future

- One case-series study examined cyanoacrylate closure in addition to compression therapy for venous leg ulcers

associated with primary varicose veins [66]. The study included 37 patients (39 legs) and reported that healing of venous leg ulcers was achieved in all cases, with an average healing time of 73.6 ± 21.9 days.

- There are also two RCT [90, 91] that evaluated cyanoacrylate closure using the Venous Clinical Severity Score (VCSS), which measures the severity of varicose veins. Although these studies focused on CEAP C4 or lower patients and did not directly assess the healing of venous leg ulcers, their findings are informative:
- Morrison et al. [90]: This study included 89 CEAP C2–C4b patients, divided into two groups: cyanoacrylate closure and radiofrequency ablation. At 60 months post-treatment, VCSS scores showed significant improvement in 75% of patients in the cyanoacrylate closure group and 73% in the radiofrequency ablation group ($p < 0.001$). Furthermore, the study assessed quality of life (QOL) using the Aberdeen Varicose Vein Questionnaire (AVVQ), reporting significant QOL improvements in both groups compared to preoperative scores (55% improvement in the cyanoacrylate group and 67% in the radiofrequency ablation group, $p < 0.001$).
- Eroglu et al. [91]: This RCT included 525 patients with primary varicose veins, who were divided into three groups: endovenous thermal ablation, radiofrequency ablation, and laser ablation. Significant reductions in VCSS scores were observed at 6 months, 1 year, and 2 years after treatment in all three groups ($p < 0.001$).
- These findings highlight the potential of cyanoacrylate closure to improve the clinical severity and QOL in patients with varicose veins. However, its specific effects on venous leg ulcer healing remain unclear and require further investigation.

5.4.4 | Incompetent Perforating Veins Are Treated at the Time of Saphenous Vein Treatment, but a Consensus Regarding the Usefulness of This Treatment for Achieving Venous Leg Ulcer Healing has Not Been Reached

- Perforating veins with reflux from deep to superficial veins are referred to as incompetent perforating veins. When performing surgery for primary varicose veins, the primary focus is typically on treating the saphenous vein. However, in some refractory cases, treatment for incompetent perforating veins is performed simultaneously.
- Historically, the Linton operation was used to treat incompetent perforating veins. This open surgical method involved ligation and dissection under direct visualization, with the incompetent perforating veins marked using ultrasonography. In recent years, minimally invasive techniques such as subfascial endoscopic perforator vein surgery (SEPS) and percutaneous ablation of perforators (PAPS) have been increasingly utilized in place of the Linton operation.
- The usefulness of treating incompetent perforating veins for the healing of venous leg ulcers has been examined in a meta-analysis of four RCTs [92]. However, these studies were limited by small sample sizes and high risk of bias, making it impossible to definitively evaluate the impact of incompetent perforating vein treatment on venous leg ulcer healing rates or associated adverse events.

5.5 | Sclerotherapy for Venous Leg Ulcers Associated With Primary Varicose Veins

Sclerotherapy is a treatment that induces venous thrombosis by chemically ablating the vascular endothelium using a sclerosing agent, leading to vein occlusion. In Japan, 0.5%, 1%, and 3% polidocanol (Polidocasclerol) are covered by health insurance for use as sclerosing agents.

5.5.1 | Sclerotherapy for Venous Leg Ulcers Associated With Primary Varicose Veins Is Classified Into Trunk Sclerotherapy and Sclerotherapy for Small Varicose Veins

- Trunk Sclerotherapy: Foam sclerotherapy has shown improved treatment outcomes [67]. This method involves mixing a sclerosing agent with air or carbon dioxide to create a foam formulation. Foam displaces intravascular blood and adheres to the vascular wall for extended periods, enabling effective treatment at lower concentrations and doses compared to liquid formulations. When treating the saphenous vein trunk with polidocanol in Japan, foam sclerotherapy using 1% or 3% polidocanol is recommended. Internationally, a phase III clinical study on foam sclerotherapy for great saphenous varices demonstrated that 83.4% of patients achieved venous occlusion and reflux resolution after 12 months, indicating superiority over liquid sclerotherapy but inferiority to surgical treatments [93]. However, this study did not specifically address venous leg ulcers.
- Sclerotherapy for Small Varicose Veins: The volume of the sclerosing agent used in this procedure is smaller than that for trunk sclerotherapy, resulting in high patient satisfaction when performed appropriately. In Japan, both liquid and foam sclerotherapy are performed using 0.5% or 1% polidocanol. For patients with venous leg ulcers caused by small varicose veins (excluding saphenous varices) or residual varicose veins after surgeries like high ligation or stripping, sclerotherapy may be a viable treatment option [81].

5.5.2 | Sclerotherapy Is Highly Safe, and Can Be Indicated for Various Varicose Veins. In the Treatment of Venous Leg Ulcers, the Healing Rate Similar to That After Surgery May Be Achieved if an Indication Criterion (Venous Diameter) is Met

- There is one RCT comparing surgery with sclerotherapy in 58 legs with venous leg ulcers and trunk reflux. It was

shown that there was no significant difference in the ulcer healing rate (100 vs. 91.3%, respectively, $p = 0.19$) [69].

- A study reported that local or superficial vein sclerotherapy for hemorrhage from the ulcer site or peripheral varicose veins led to hemostasis [94]. This is applied as a simple method in clinical practice.
- Most complications related to sclerotherapy are mild. Primary complications include intra-aneurysmal thrombosis, telangiectatic matting (microangiogenesis after sclerotherapy), pigmentation, pain, allergy, and urticaria [95]. A study showed that the incidence of serious adverse events, such as pulmonary embolism and DVT, was ≤1% in 9000 patients treated by foam sclerotherapy [96]. Furthermore, foam sclerotherapy-specific complications include transient visual impairment, cerebral ischemic attacks, pressure in chest, and dry cough.

5.6 | Evaluation of Treatment

5.6.1 | When Evaluating Treatment, an Improvement in Preoperative Symptoms Is the Most Important

- Evaluation through inquiry is essential. Improvement in pretreatment symptoms or complaints serves as the best parameter for assessing treatment efficacy. For venous leg ulcers, treatment can be evaluated based on ulcer healing or reduction. However, since ulcers may recur, regular follow-up is necessary.

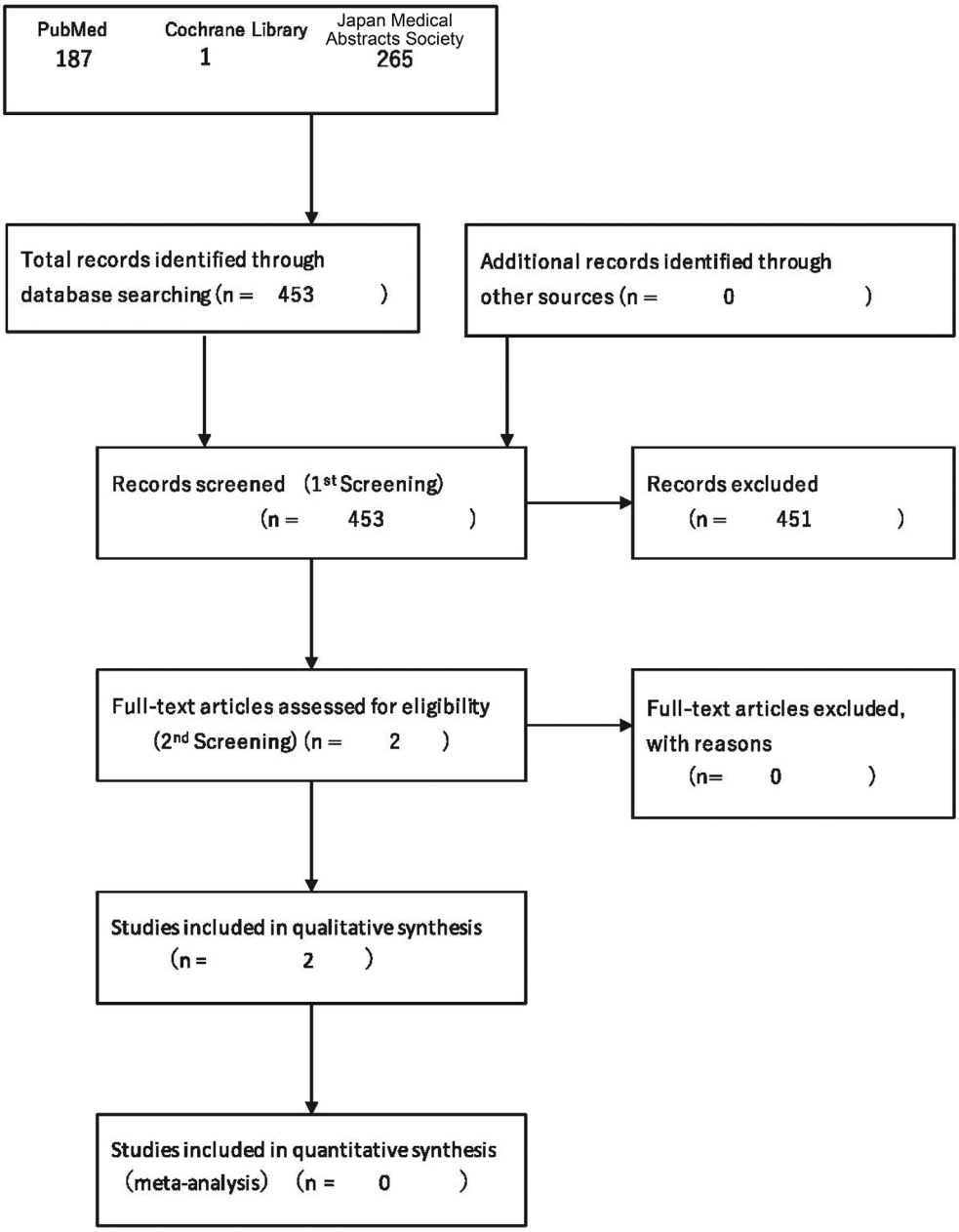


FIGURE 12 | Ultrasonography for varicose veins: Flowchart of literature search.

5.6.2 | Evaluation of Treatment Using Simple Examinations

- For postoperative assessment following surgery for varicose veins, auscultation with a Doppler auscultator to check for the presence or absence of superficial venous reflux is simple and highly recommended.
- If plethysmography, such as air plethysmography (APG), is available, treatment outcomes can be objectively evaluated by comparing pre- and postoperative data.

5.6.3 | Evaluation of Treatment Using Imaging Procedures

- Ultrasonography is frequently selected for postoperative evaluation. It allows assessment of the inhibition of venous reflux after treatment and can diagnose recurrence due to incompetent perforating veins.
- For long-term evaluation of the entire leg post-surgery, MR venography (MRV) is appropriate. Three-dimensional (3D) images reconstructed from MRV data facilitate

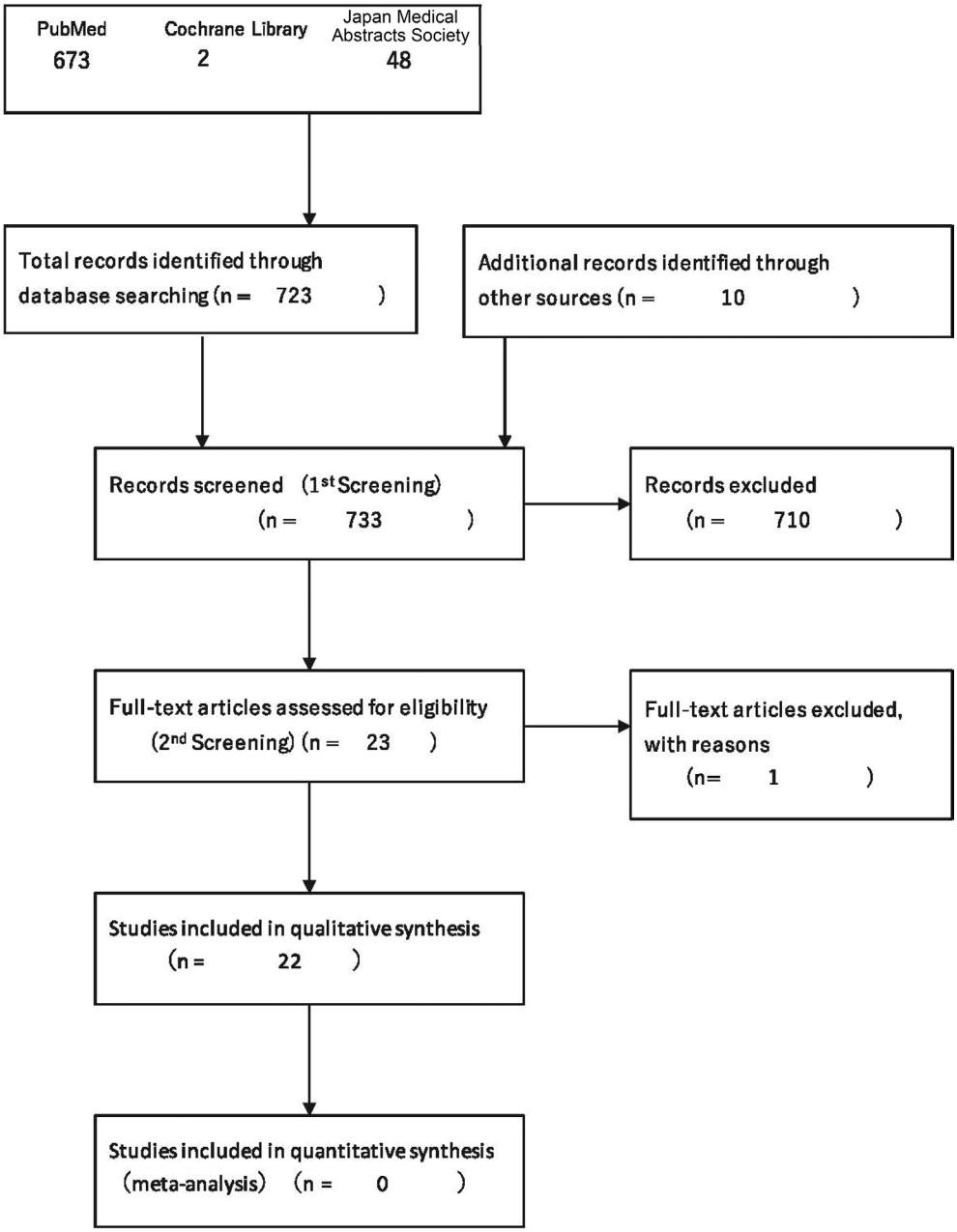


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FIGURE 13 | Ultrasonography for DVT: Flowchart of literature search.

CQ	1	Is ultrasonography recommended for the diagnosis of venous leg ulcers?
P	Patients in whom varicose veins and deep vein thrombosis are suspected as etiological factors for venous leg ulcers or those with the risks of these disorders. Ultrasonography refers to color Doppler-combined duplex ultrasonography or compression ultrasonography.	
I	Patients in whom ultrasonography was performed.	
C	Venography	
Clinical context	Diagnosis	

1	Diagnosis of varicose veins using ultrasonography
Indirectness	Neither the diagnostic sensitivity nor specificity of ultrasonography for varicose veins has been shown. For diagnosis, it is important to rule out the possibility of secondary varicose veins, and its diagnostic sensitivity/specificity for deep vein thrombosis are necessary. The indirectness was evaluated as “high (-2)”.
Bias risk	This was a retrospective observational study from a single institution, and the bias risk was evaluated as “high (-2)”.
Inconsistency and others	There was a single study, and there was no inconsistency. The inconsistency was evaluated as (0).
Comments	As there is no description on sensitivity/specificity, evaluation is impossible.

2	Diagnosis of DVT using ultrasonography
Indirectness	In some references, venography as a gold standard for DVT diagnosis was not compared with ultrasonography, and the sensitivity/specificity may not have been accurate. Therefore, the indirectness was evaluated as “high (-2)”.
Bias risk	There were differences in the target population among the references. Blinding was impossible due to some symptoms, and the bias risk was evaluated as “high (-2)”.
Inconsistency and others	There was inexplicable heterogeneity on the results, and the inconsistency was evaluated as “high (-2)”.
Comments	The bias risk was high, and the certainty of evidence was evaluated as D (very weak).

FIGURE 14 | Ultrasonography Qualitative systematic review.

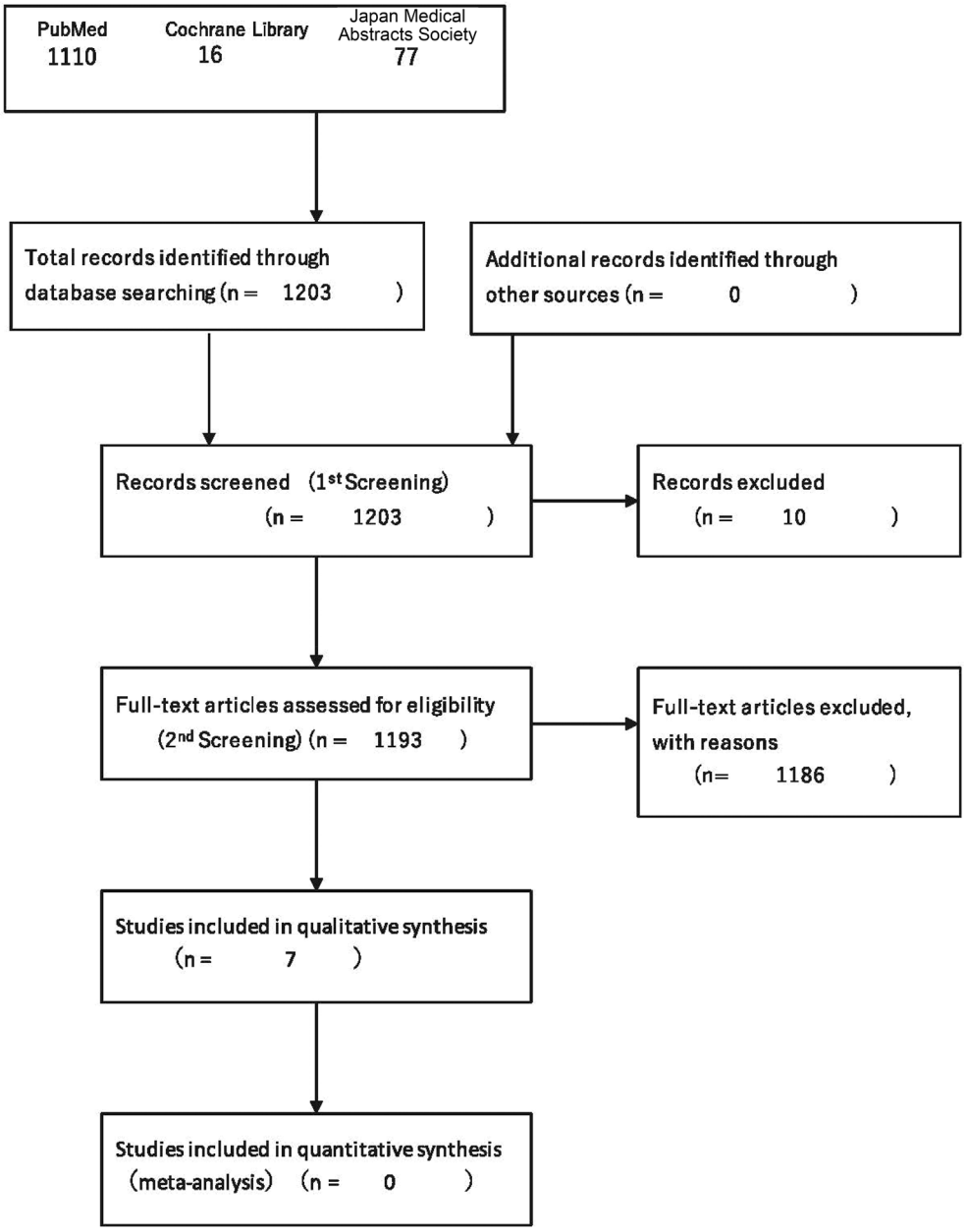

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FIGURE 15 | Compression therapy for venous ulcers of the lower leg: Flowchart of literature search.

intuitive assessments. However, clear imaging may not be possible in cases of leg edema, swelling, marked inflammation, recurrent ulcers, or after artificial joint replacement.

5.6.4 | Posttreatment Evaluation of Post-Thrombotic Syndrome (PTS)

- Posttreatment evaluation of PTS includes visual inspection of symptom improvements and assessment of superficial venous reflux or upflow using a Doppler auscultator. In many cases, serial leg circumference measurements can also be used to evaluate symptom changes, although this method is slightly complex. As with primary varicose veins, serial APG measurements, ultrasonography, and MRV are recommended for PTS assessment.
- For further evaluation of PTS, serial D-dimer levels and coagulation-system parameters obtained through blood tests are recommended. These should be monitored regularly.

5.6.5 | Evaluation in Patients Treated by Compression Therapy Alone

- In cases where follow-up is performed after conservative treatment, including compression therapy alone, improvements in symptoms or ulcers should be assessed.

[SR-7 evaluation sheet, total evidence]

Treatment guidelines	Guidelines for the management of lower leg ulcers/varicose veins, 3rd edition
Subjects	Patients with venous ulcers of the lower leg
Intervention	Compression therapy
Control	No compression therapy

*Bias risk, indirectness
Each domain is evaluated in 3 grades: "high (-2)", "medium/suspected (-1)", and "low (0)".
A summary is reflected to total evidence in 3 grades: "high (-2)", "medium (-1)", and "low (0)".

** Factors for elevation
Each item is evaluated in 3 grades: "high (+2)", "medium (+1)", and "low (0)".
A summary is reflected to total evidence in 3 grades: "high (+2)", "medium (+1)", and "low (0)".

The results for each outcome are summarized in appendices.

Total evidence

Outcome	Study design/Number of studies	*Bias risk	*Inconsistency	*Inaccuracy	*Indirectness	*Others (such as publication bias)	*Factors for elevation (observational study)	Number at risk (Outcome rate): Denominator in the control group	Numerator in the control group	(%)	Denominator in the intervention group	Numerator in the intervention	(%)	Effect measure (kind)	Integrated value of measures	95% confidence interval	**Strength of evidence	***Importance	Comment
Ulcer-healing rate	RCT/3	-2	0	0	-1	0	0	80	25	31.3	79	42	53.2	RR	4.00	2.03, 7.85	D	5	Blinding was impossible, and the bias risk was evaluated as -2.

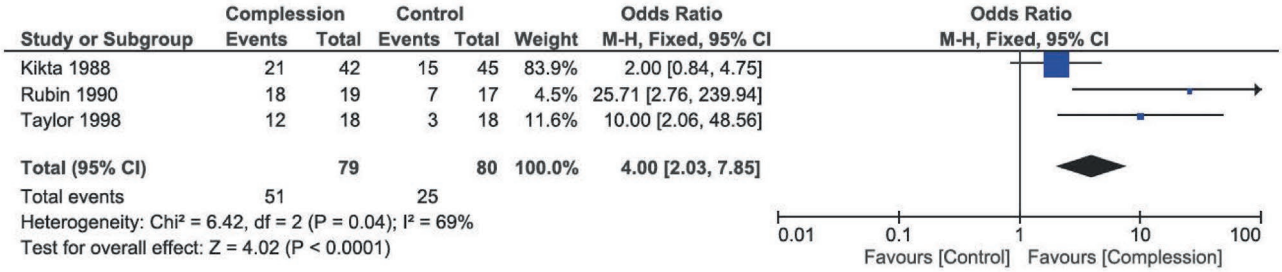


FIGURE 16 | Compression therapy.

As described above, evaluations should also include examinations such as Doppler auscultation and imaging procedures.

- For "cramps," a common symptom in moderate or severe cases, treatments with Shakuyakukanzoto have been reported [100].

5.7 | Combination Therapy

Some studies have reported that the addition of certain Chinese herbal medicines to compression therapy for primary varicose veins or DVT can be effective.

- Primarily, improvements in symptoms have been reported. Several studies have described the efficacy of treatments with Keishibukuryogan [97, 98] and one report explored combination therapy using Keishibukuryogan, Goreisan, and Saireito [99].

6 | Chapter 6 Data and Analyses of CQs

CQ1 Is Ultrasonography Recommended for the Diagnosis of Venous Leg Ulcers?

Recommendation	Strength	Certainty of evidence
We propose to perform ultrasonography for the diagnosis of venous leg ulcers.	Weak	Very weak

CQ	2	Is compression therapy recommended for the treatment of lower leg ulcers associated with primary or secondary varicose veins?
P	Venous leg ulcers associated with primary or secondary varicose veins	
I	Compression therapy	
C	No compression therapy	
Clinical context	Treatment	

1	Ulcer recurrence rate
Indirectness	There was no indirectness, and the indirectness was evaluated as "low (0)".
Bias risk	Blinding with respect to the presence or absence of compression therapy was impossible, and the bias risk was evaluated as "high (-2)".
Inconsistency and others	There was a single study, and there was no inconsistency. The inconsistency was evaluated as "low (0)".
Comments	An adequate observation period was unclear. Blinding was impossible, and the strength of total evidence was evaluated as D (very weak).

FIGURE 17 | Compression therapy Qualitative systematic review.

6.1 | Literature Search

For the third edition of the Guidelines for the management of lower leg ulcers/varicose veins, the Japan Medical Library Association searched the electronic databases PubMed, Cochrane Library, and Japanese Medical Abstracts Society to identify the relevant clinical trials published between January 1980 and December 2020.

Results: With respect to varicose veins, clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were selected in PubMed, and 187 studies were found. In the Cochrane Library, 1 study was found. In the Japan Medical Abstracts Society, 265 studies were found, excluding case reports/meeting minutes. Of these, primary screening was performed in 453. With respect to DVT, clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were selected in PubMed, and 673 studies were found. In the Cochrane Library, 2 studies were found. In the Japan Medical Abstracts Society, 48 studies were found, excluding case reports/meeting minutes. Ten similar articles were added, and primary screening was performed in 723 studies.

6.2 | Outcome

The systematic review team selected the sensitivity and specificity of ultrasonography for varicose veins and DVT (Importance: 5) as an outcome. The relative importance of the outcome was voted on by all drafting committee members, with 100% agreement.

6.3 | Literature Screening

Concerning varicose veins, primary screening was performed, and two studies were selected. There was no description on sensitivity/specificity, and there were only comments; therefore, recommendations for CQ1 were primarily reviewed with respect to DVT. Concerning DVT, primary screening was performed, and 23 studies were selected. As secondary screening, 22 were adopted, excluding 1 article in which neither the sensitivity nor specificity of ultrasonography could be calculated.

A flow chart of literature search is presented (Figures 12 and 13).

6.4 | Evaluation of Certainty of Evidence

A method of evaluating varicose veins using ultrasonography was reported, and there was no description of its diagnostic accuracy. There was only 1 article describing that venography was required due to insufficient ultrasonography findings in 15% of patients and 1 commentary.

With respect to the 22 articles selected on secondary screening of DVT, the selection bias, performance bias, detection bias, attrition bias, and other biases were assessed based on the Minds Manual for Guideline Development 2020 ver. 3.0.

6.5 | Evaluation of the Outcome

There were no significant data on the diagnosis of varicose veins. Concerning the diagnosis of DVT, the sensitivity and specificity were summarized for reference from the results of each report.

6.6 | Results

There was no description on the diagnostic sensitivity or specificity of ultrasonography for varicose veins. A meta-analysis could not be performed. Concerning DVT, a qualitative systematic review was performed (Figure 14).

Certainty of evidence: Very weak (D).

Based on these results, a summary of the results (SoF) was prepared and presented at a panel meeting.

CQ2 Is Compression Therapy Recommended for the Treatment of Venous Leg Ulcers Associated With Primary or Secondary Varicose Veins?

Recommendation	Strength	Certainty of evidence
We propose to perform compression therapy for lower leg ulcers associated with primary or secondary varicose veins.	Weak	Very weak

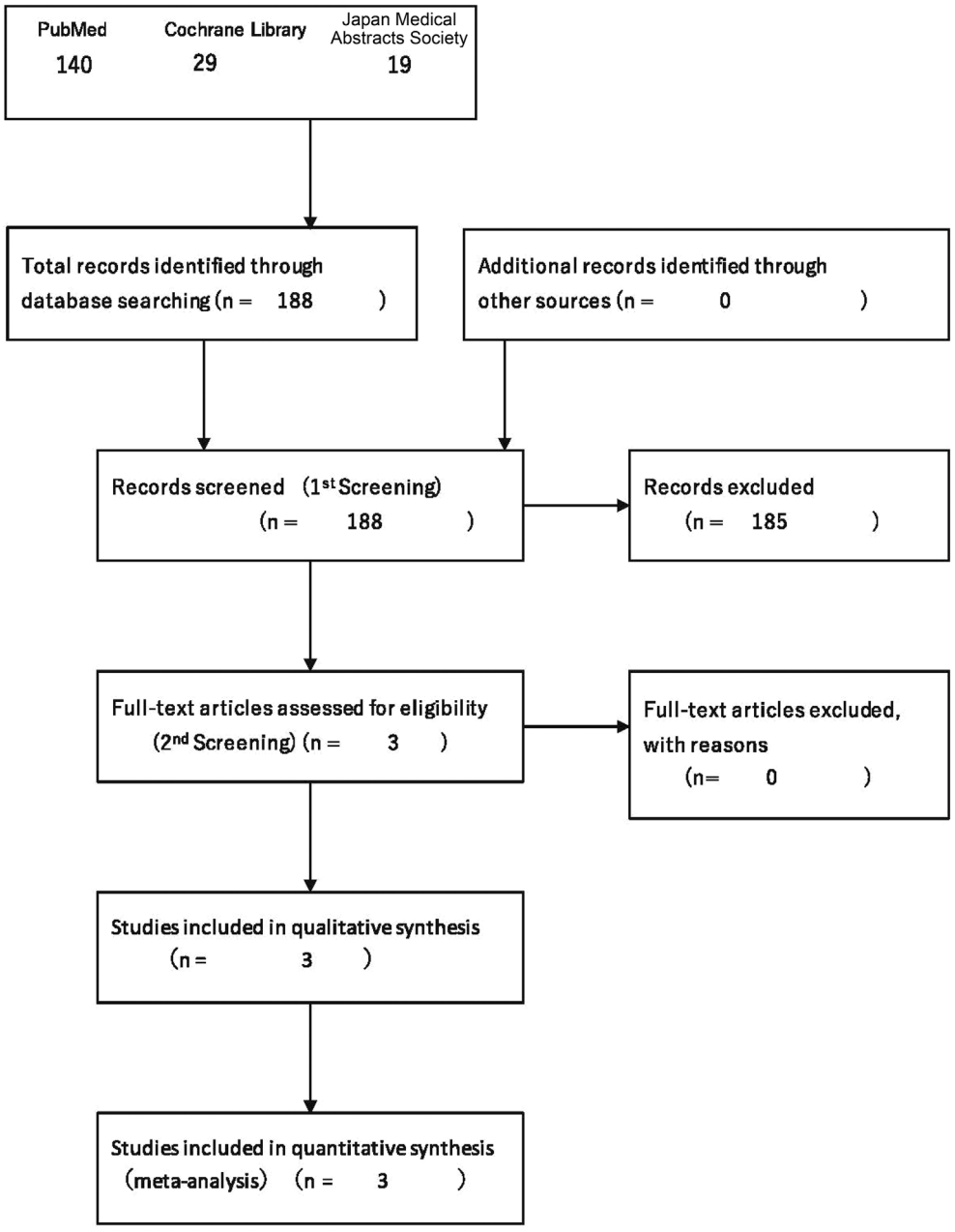


FIGURE 18 | Surgery: Flowchart of literature search.

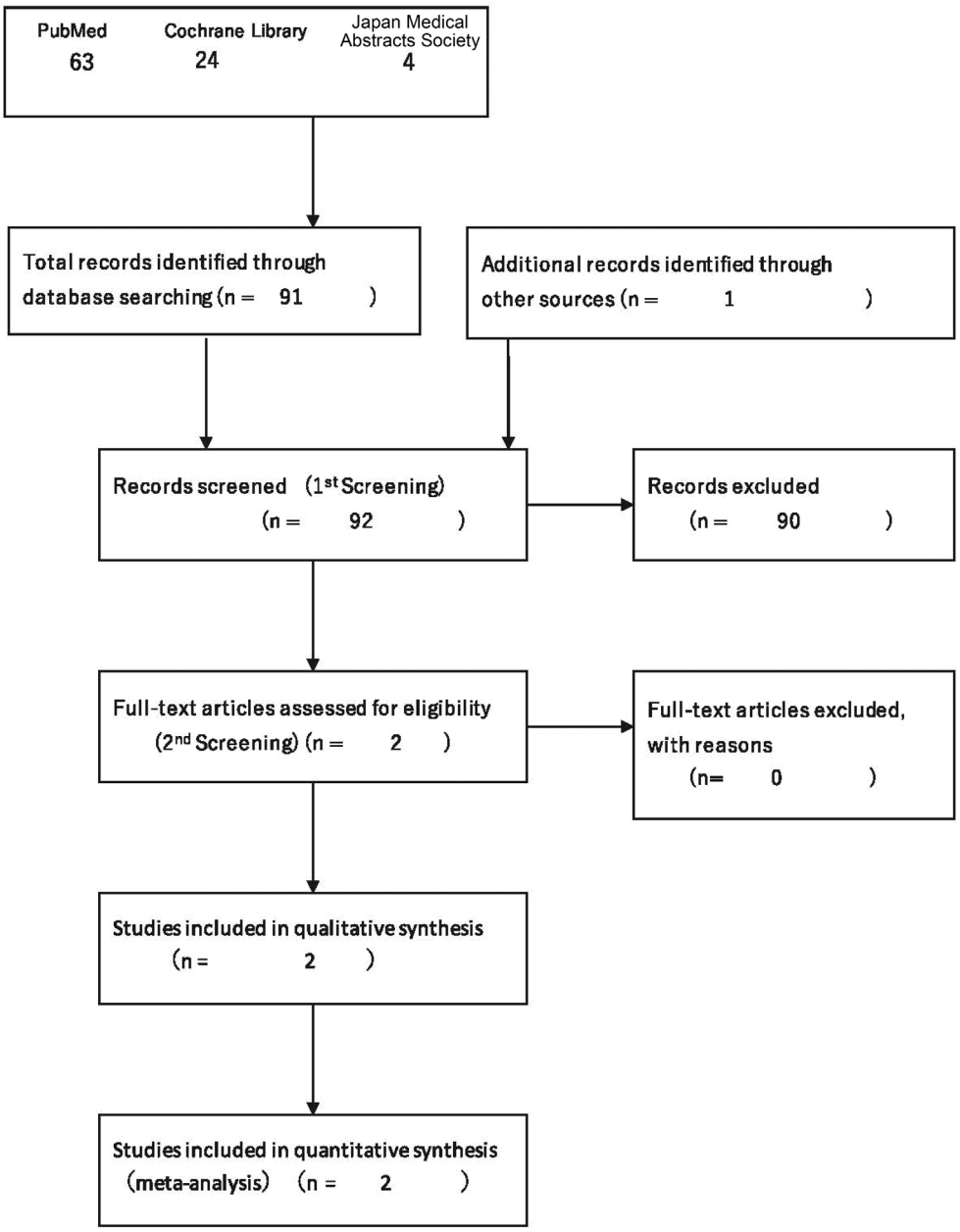
6.7 | Literature Search

For the third edition of the Guidelines for the management of lower leg ulcers/varicose veins, the Japan Medical Library Association searched the electronic databases PubMed, Cochrane Library, and Japanese Medical Abstracts Society to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search appeared in Supporting Information, which can be obtained from the Japanese Dermatological Association.

PubMed: 1110 studies, Cochrane Library: 16, and Japan Medical Abstracts Society: 77 were found. Of these, 1 article in PubMed was published after 2021, and 9 were duplicated among the databases. From 1193 studies, excluding them, clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were selected, and primary screening was performed, excluding case reports/meeting minutes.

6.8 | Outcome

The systematic review team selected the healing rate in a specific period (1) and the recurrence rate (2) (Importance: 5) as outcomes. The relative importance of the outcomes was voted on by all drafting committee members, with 100% agreement.



Prepared using a template of the Minds Manual for Guideline Development 2020 ver. 3.0.

FIGURE 19 | Endovenous thermal ablation: Flowchart of literature search.

6.9 | Literature Screening

On primary screening, case reports or reviews, abstract-free articles, articles with no relationship to venous leg ulcers, research articles, and articles that do not correspond to systematic reviews were excluded based on abstracts, and 40 studies were selected. In these, secondary screening was performed. On secondary screening, among the articles obtained, clinical studies of compression therapy for venous leg ulcers associated with primary or secondary varicose veins were extracted, and 7 articles were selected. A flow chart of literature search is presented (Figure 15).

6.10 | Evaluation of Certainty of Evidence

With respect to the 3 RCTs selected on secondary screening, the selection bias, performance bias, detection bias, attrition bias, and other biases were assessed based on the Minds Manual for Guideline Development 2020 ver. 3.0. Due to the

[SR-7 evaluation sheet, total evidence]

Treatment guidelines	Guidelines for the management of lower leg ulcers/varicose veins, 3rd edition
Subjects	Patients with venous ulcers of the lower leg
Intervention	Surgery + compression therapy
Control	Compression therapy

*Bias risk, indirectness

Each domain is evaluated in 3 grades: "high (-2)", "medium/suspected (-1)", and "low (0)".

A summary is reflected to total evidence in 3 grades: "high (-2)", "medium (-1)", and "low (0)".

** Factors for elevation

Each item is evaluated in 3 grades: "high (+2)", "medium (+1)", and "low (0)".

A summary is reflected to total evidence in 3 grades: "high (+2)", "medium (+1)", and "low (0)".

The results for each outcome are summarized in appendices.

Total evidence

Outcome	Study design/Number of studies	* Bias risk	* Inconsistency	* Inaccuracy	*Indirectness	* Others (such as publication bias)	* Factors for elevation (observational	Number at risk (Outcome rate) Denominator in the control group	Numerator in the control group	(%)	Denominator in the intervention group	Numerator in the intervention group	(%)	Effect measure (kind)	Integrated value of effect measures	95% confidence interval	** Strength of evidence	*** Importance	Comment
Ulcer-healing rate	RCT/3	-2	0	0	-1	0	0	385	323	83.9	362	317	87.6	RR	1.04	0.98-1.11	D	5	No difference.

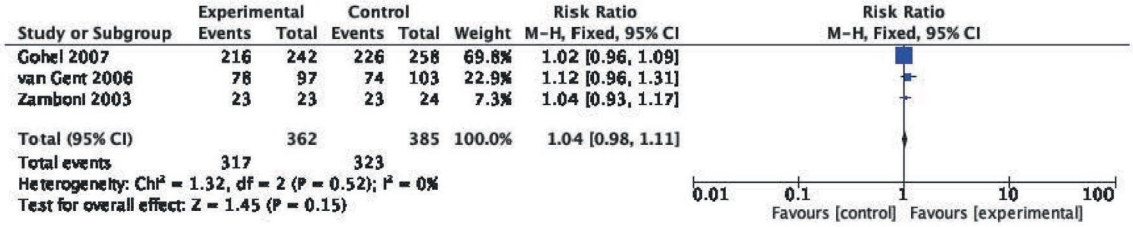


FIGURE 20 | High ligation/stripping.

procedure of compression therapy, blinding of performance and detection was impossible, and these were evaluated as having a bias.

6.11 | Evaluation of the Outcome

A meta-analysis was performed for the respective outcome in relative effect and 95% confidence interval with Review Manager Version 5.4, The Cochrane Collaboration, 2020.

6.12 | Results

Ulcer-healing rate: Relative effect: 4.00, 95% confidence interval, 2.03 to 7.85, Certainty of evidence: Very weak (D).

Concerning the ulcer recurrence rate, a qualitative systematic review was performed.

When preparing an explanatory text for CQ2, it was determined to describe general principles and precautions for use in addition to the quantitative assessment of compression therapy. The forest plot of each outcome and total evidence are shown (Figures 16 and 17) (with respect to assessment sheets for each outcome, refer to Supporting Information).

Based on these results, a summary of the results (SoF) was prepared and presented at a panel meeting.

CQ3 Is Surgical Therapy Recommended for the Treatment of Venous Leg Ulcers Associated With Primary Varicose Veins?

Recommendation	Strength	Certainty of evidence
We propose to perform stripping of the saphenous vein/high ligation or endovenous thermal ablation (laser, radiofrequency) for the treatment of venous leg ulcers associated with primary varicose veins.	Weak	Very weak

[SR-7 evaluation sheet, total evidence]

Treatment guidelines	Guidelines for the management of lower leg ulcers/varicose veins, 3rd edition
Subjects	Patients with venous ulcers of the lower leg
Intervention	Surgery + compression therapy
Control	Compression therapy

*Bias risk, indirectness
Each domain is evaluated in 3 grades: "high (-2)", "medium/suspected (-1)", and "low (0)".
A summary is reflected to total evidence in 3 grades: "high (-2)", "medium (-1)", and "low (0)".

** Factors for elevation
Each item is evaluated in 3 grades: "high (+2)", "medium (+1)", and "low (0)".
A summary is reflected to total evidence in 3 grades: "high (+2)", "medium (+1)", and "low (0)".

The results for each outcome are summarized in appendices.

Total evidence

Outcome	Study design/Number of studies	* Bias risk	* Inconsistency	* Inaccuracy	*Indirectness	* Others (such as publication bias)	* Factors for elevation (observational study)	Number at risk (Outcome rate) Denominator in the control group	Numerator in the control group	(%)	Denominator in the intervention group	Numerator in the intervention	(%)	Effect measure (kind)	Integrated value of effect measures	95% confidence interval	** Strength of evidence	*** Importance	Comment
Ulcer-healing rate	RCT/2	-2	0	0	-1	0	0	254	196	77.2	250	217	86.8	RR	1.12	1.04-1.22	D	5	There is a bias.

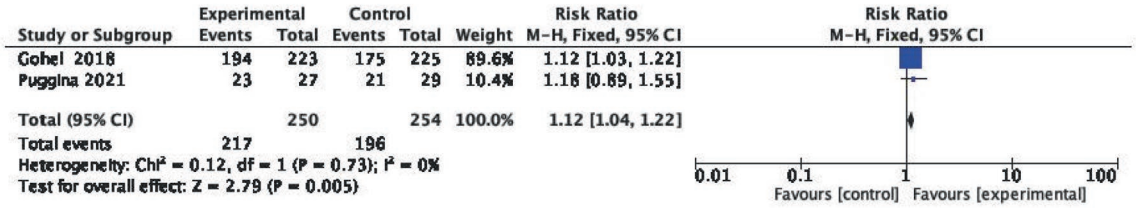


FIGURE 21 | Endovenous thermal ablation.

6.13 | Literature Search

For the third edition of the Guidelines for the management of lower leg ulcers/varicose veins, the Japan Medical Library Association searched the electronic databases, PubMed, Cochrane Library, and Japanese Medical Abstracts Society to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search appeared in Supporting Information which can be obtained from the Japanese Dermatological Association.

High ligation/stripping PubMed: 140 studies, Cochrane Library: 29, and Japan Medical Abstracts Society: 19 were found. Of these, clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were selected, and primary screening was performed in 188 studies, excluding case reports/meeting minutes.

Endovenous thermal ablation PubMed: 63 studies, Cochrane Library: 24, and Japan Medical Abstracts Society: 4 were found. Of these, clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were selected, and primary screening was performed in 92 studies, excluding case reports/meeting minutes.

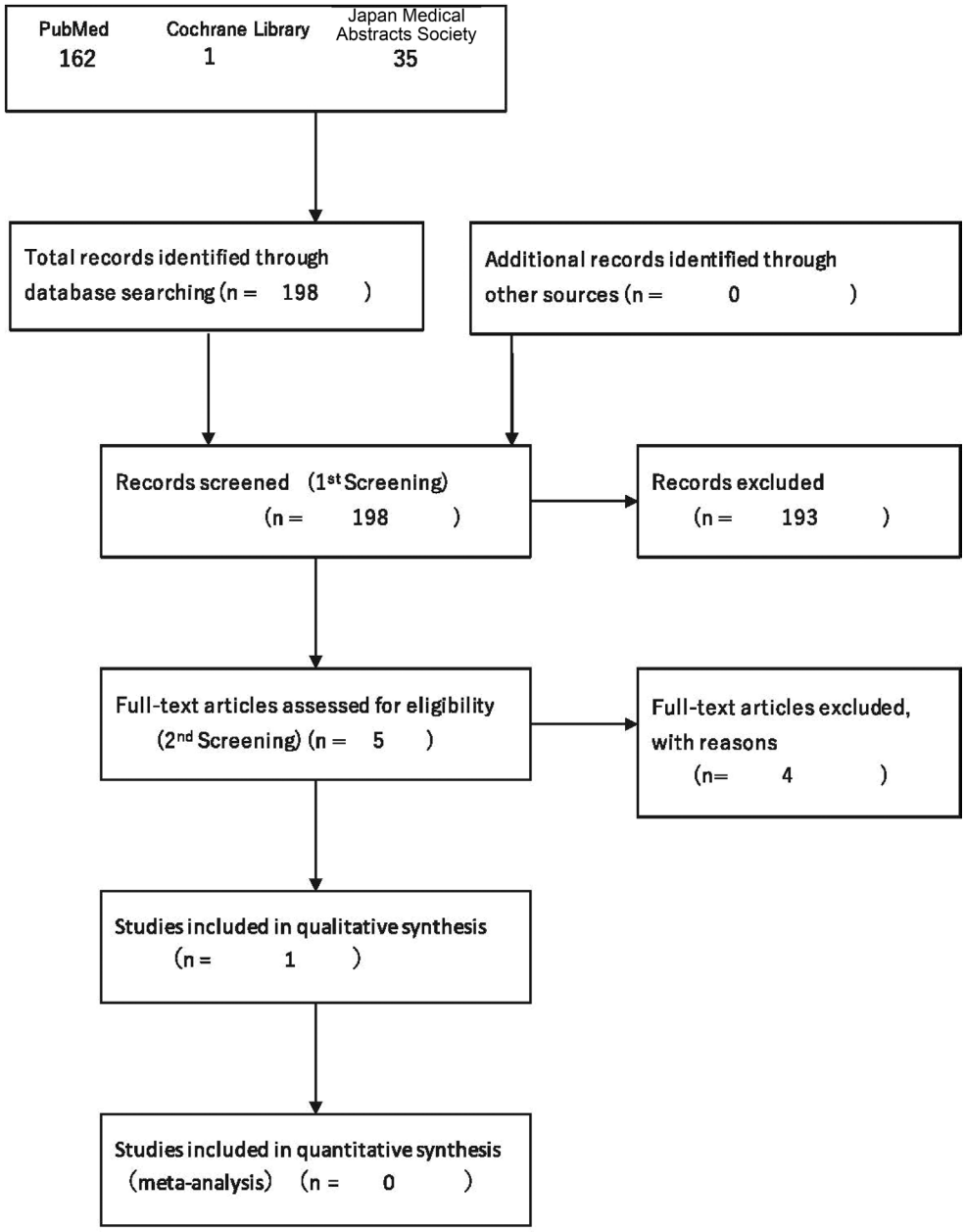
6.14 | Outcome

The systematic review team selected Ulcer-healing rate (Importance: 5) as an outcome. The relative importance of the outcome was voted on by all drafting committee members, with 100% agreement.

6.15 | Literature Screening

High ligation/stripping Primary screening was performed, and 188 studies were selected. Of these, three remained after secondary screening. Finally, three in which the healing rate of lower leg ulcers associated with primary varicose veins was evaluated remained.

Endovenous thermal ablation Primary screening was performed, and 92 studies were selected. Of these, two remained



Prepared using a template of the Minds Manual for Guideline Development 2020 ver. 3.0.

FIGURE 22 | Sclerotherapy for venous ulcers of the lower leg: Flow chart of literature search.

on secondary screening. Finally, two in which the healing rate of lower leg ulcers associated with primary varicose veins was evaluated remained.

A flow chart of literature search is presented (Figures 18 and 19).

6.16 | Evaluation of Certainty of Evidence

With respect to the three RCTs selected on secondary screening, the selection bias, performance bias, detection bias, attrition bias, and other biases were assessed based on the Minds Manual for Guideline Development 2020 ver. 3.0.

6.16.1 | Evaluation of the Outcome

With respect to high ligation/stripping and endovenous thermal ablation, a meta-analysis regarding the ulcer-healing rate was performed. For outcome assessment, the integrated value and 95% confidence interval of effect measures for respective outcomes were calculated using Review Manager 5.4.

6.16.2 | Results

Ulcer-healing rate: The integrated value and 95% confidence interval of effect measures for high ligation/stripping were 1.04 and 0.98 to 1.11, respectively. The strength of evidence

was established as very weak (D). The integrated value and 95% confidence interval of effect measures for endovenous thermal ablation were 1.12 and 1.04 to 1.22, respectively. The strength of evidence was established as very weak (D). The forest plot of each outcome and total evidence are shown (Figures 20 and 21). (with respect to assessment sheets for each outcome, refer to Supporting Information).

Based on these results, a summary of the results (SoF) was prepared and presented at a panel meeting.

CQ4 Is Sclerotherapy Recommended for the Treatment of Lower Leg Ulcers Associated With Varicose Veins?

Recommendation	Strength	Certainty of evidence
We propose to perform sclerotherapy for lower leg ulcers associated with varicose veins.	Weak	Very weak

6.17 | Literature Search

For the third edition of the Guidelines for the management of lower leg ulcers/varicose veins, the Japan Medical Library Association searched the electronic databases PubMed, Cochrane Library, and Japanese Medical Abstracts Society to identify the relevant clinical trials published between January 1980 and December 2020. Details of the literature search appeared in Supporting Information which can be obtained from the Japanese Dermatological Association.

PubMed: 162 studies, Cochrane Library: 1, and Japan Medical Abstracts Society: 35 were found. Of these, clinical trials, meta-analyses, randomized controlled trials, and systematic reviews were selected, and primary screening was performed in a total of 19 studies: PubMed, 5; Japan Medical Abstracts Society, 14; and Cochrane Library, 1, excluding case reports/meeting minutes.

6.18 | Outcome

The systematic review team selected Ulcer-healing rate (Importance: 5), Incidence of complications (Importance: 5) and Improvement in the QOL (Importance: 5) as outcomes. The relative importance of outcomes was voted on by all drafting committee members, with 100% agreement.

6.19 | Literature Screening

Based on the results of primary screening, secondary screening was performed in PubMed: 5 studies. Two examining the effects of endovenous thermal ablation were excluded. One describes the venous occlusion rate after sclerotherapy in sclerotherapy + compression therapy and compression therapy-free

CQ	4	Is sclerotherapy recommended for the treatment of lower leg ulcers associated with varicose veins?
P	Patients with active ulcers associated with varicose veins	
I	Sclerotherapy	
C	Surgical treatment	
Clinical context	Treatment: The ulcer-healing rates for surgical treatment and sclerotherapy were high, with no significant difference.	

1	Ulcer-healing rate
Indirectness	As the patients in the literature were not Japanese, the indirectness was evaluated as "medium (-1)".
Bias risk	In the study, blinding was impossible. At baseline, the ulcer size in the surgical treatment group was larger than in the sclerotherapy group; there was a bias. The bias risk was evaluated as "high (-2)".
Inconsistency and others	Due to a single study, there was no inconsistency. The inconsistency was evaluated as "low (0)".
Comments	Thus, the strength of total evidence was evaluated as D (very weak).

2	Incidence of complications
Indirectness	As the patients in the literature were not Japanese, the indirectness was evaluated as "medium (-1)".
Bias risk	In the single-center study, blinding was impossible. The bias risk was evaluated as "high (-2)".
Inconsistency and others	Due to a single study, there was no inconsistency. The inconsistency was evaluated as "low (0)".
Comments	The incidences of general adverse events in the sclerotherapy and surgical treatment groups were 13 and 14.2%, respectively (p=1.0). There was no serious complication. This is consistent with the results of other study reports describing that serious adverse events are rare (0' Haro 2008). However, the strength of total evidence was evaluated as D (very weak).
3	QOL improvement
Indirectness	As the patients in the literature were not Japanese, the indirectness was evaluated as "medium (-1)".
Bias risk	In the single-center study, blinding was impossible. The bias risk was evaluated as "high (-2)".
Inconsistency and others	Due to a single study, there was no inconsistency. The inconsistency was evaluated as "low (0)".
Comments	Concerning an improvement in the QOL, the Aberdeen Varicose Vein Questionnaire (AVVQ), Venous Clinical Severity Score (VCSS), and Venous Disability Score (VDS) were filled out before and after treatment. Both sclerotherapy and surgical treatment improved the scores. Thus, the strength of total evidence was evaluated as D (very weak).

FIGURE 23 | Sclerotherapy Qualitative systematic review.

sclerotherapy groups. In the two groups, the venous occlusion rates were high, suggesting the effects of sclerotherapy. However, there is no description of the presence or absence of ulcers in the subjects or effects on ulcer healing; this study was excluded. Only the remaining 2 studies investigated the healing rate of venous ulcers of the lower leg after sclerotherapy. In one of these, the results did not suggest the efficacy of sclerotherapy. Only the other was finally adopted. A flow chart of literature search is presented (Figure 22).

6.20 | Evaluation of Certainty of Evidence

The finally adopted study represents a prospective randomized study comparing surgical treatment with sclerotherapy in patients with lower leg ulcers associated with varicose veins. The number of patients was 28 in the surgical treatment group and 23 in the sclerotherapy group, which is small. However, the ulcer-healing rate, incidence of complications, and an improvement in the QOL were statistically examined.

6.21 | Evaluation of Outcome

Concerning the "ulcer-healing rate", survival curves were compared using the Kaplan–Meier method and log-rank test. It is described that there was no significant difference between surgical treatment and sclerotherapy, and that a high healing rate was achieved. Concerning the QOL, statistical analysis was also performed, and it is described that the two treatments showed significant improvement ratings. Concerning "complications", there was no serious complication.

6.22 | Results

Only 1 study was adopted, and the number of patients was 23, being small. Therefore, a meta-analysis was not performed, and a qualitative systematic review was performed (Figure 23).

Based on these results, a summary of the results (SoF) was prepared and presented at a panel meeting.

Conflicts of Interest

The authors declare no conflicts of interest.

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Appendix 1

Wound/Pressure Ulcer/Burn Guidelines Drafting Committee Member List

Supervising Committee

Chairperson: Takao TACHIBANA (Hoshigaoka Medical Center).

Vice-chairperson: Minoru HASEGAWA (University of Fukui), Manabu FUJIMOTO (Osaka University).

Members: Yoshihide ASANO (Tohoku University), Takeshi NAKANISHI (Meiji University of Integrative Medicine), Hiroshi FUJIWARA (Niigata University), Takeo MAEKAWA (Jichi Medical University Saitama Medical Center), Sei-ichiro MOTEGI (Gunma University), Yuichiro YOSHINO (Japanese Red Cross Kumamoto Hospital).

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Wounds in General

Sei-ichiro MOTEGI (Gunma University), Masaru ARIMA (Fujita Health University), Toshio ICHIKI (Kyushu University), Ikuko UEDA-HAYAKAWA (Osaka University), Katsuyuki OKADA (Kiryu Kosei General Hospital), Sakae KANEKO (Japanese Red Cross Masuda Hospital), Hiroyuki KANO (Gifu Municipal Hospital), Yuta KURASHIGE (Kurashige Dermatology Clinic), Akira SHIMIZU (Kanazawa Medical University), Yasuyuki SUMIKAWA (Hokutoukai Sumikawa Dermatology Allergy Clinic), Hidenori TAKAHASHI (Japan Community Health care Organization (JCHO) Fukui Katsuyama General Hospital), Zenshiro TAMAKI (Saitama Children's Medical Center), Michio TOKUYAMA (Tokai University), Hideki FUJITA (Nihon University), Koji HABE (Mie University).

Pressure Ulcers

Hiroshi FUJIWARA (Niigata University), Ryokichi IRISAWA (Tokyo Medical University), Masaki OTSUKA (Chutoen General Medical Center), Tomoko KAKO (Mie Prefectural General Medical Center), Tatsuya KAJI (Hiroshima City Hiroshima Citizens Hospital), Takafumi KADONO (St. Marianna University School of Medicine), Monji KOGA (Fukuoka University), Kuninori HIROSAKI (Hokkaido Medical Center).

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Takeshi NAKANISHI (Meiji University of Integrative Medicine), Ryuta IKEGAMI (Ikegami Clinic), Shun OMORI (Kokura Daiichi Hospital), Hiroshi KATO (Nagoya City University), Satoshi KOMORI (Kyoto Prefectural University of Medicine), Tomomichi SHIMIZU (Tokai University), Kazunari SUGITA (Saga University), Hideaki TANIZAKI (Kansai Medical University), Hideki NAKAJIMA (Kochi University), Shujiro HAYASHI (Dokkyo Medical University), Risa MATSUO (Asahikawa Medical University), Hiroshi MITSUI (University of Yamanashi), Hiroto YANAGISAWA (Saitama Medical University), Michiya YAMAGUCHI (Yamaguchi University), Osamu YAMASAKI (Shimane University).

Connective Tissue Diseases and Vasculitis

Yoshihide ASANO (Tohoku University), Jun ASAI (Kyoto Prefectural University of Medicine), Takayuki ISHII (Toyama Prefectural Central Hospital), Yohei IWATA (Fujita Health University), Akihiko UCHIYAMA (Gunma University), Ken OKAMURA (Yamagata University), Yoichi OGAWA (University of Yamanashi), Mari KISHIBE (Asahikawa Medical University), Yuta KOIKE (Nagasaki University), Masanari KODERA (Japan Community Health care Organization (JCHO) Chukyo Hospital), Yorihisa KOTOBUKI (Kotobuki Dermatology Clinic), Noriki FUJIMOTO (Shiga University of Medical Science), Takuya MIYAGI (University of the Ryukyus), Chie MIYABE (Tokyo Women's Medical University), Yukie YAMAGUCHI (Yokohama City University), Ayumi YOSHIZAKI (The University of Tokyo).

Leg Ulcers/Varices

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Appendix 2

Declarations of Interest

Conflict of interest (COI) reporting criteria for participants in the Wound/Pressure Ulcer/Burn Guidelines Supervising and Drafting Committees, participation/non-participation criteria, and a list of the COI disclosed (Prepared in reference to JAMS Guidelines on COI Management in Medical Research (in March 2017, Japanese Association of Medical Sciences, https://jams.med.or.jp/guideline/index.html)).

Criteria for Judgment of COI Disclosure

Participants

1. Presence or absence of officers and advisors in companies and for-profit organizations and the amounts of their remunerations.

Classification of pension amounts: (1) equal to or more than1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than10 million yen/company/year.

2. Ownership of stocks and profits derived from the stocks (profits for the previous year presented in this format).

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

3. Royalty payments for patents by companies and for-profit organizations.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

4. Remunerations, such as daily allowances and lecture fees, paid by a company and for-profit organization for attending a conference (presentations, advice).

Classification of amount: (1) equal to or more than 0.5 million yen/company/year, (2) equal to or more than 1 million yen/company/year, (3) equal to or more than 2 million yen/company/year

5. Fees paid by a company and for-profit organization for the creation of pamphlets and roundtable discussion articles.

Classification of amount: (1) equal to or more than 0.5 million yen/company/year, (2) equal to or more than 1 million yen/company/year, (3) equal to or more than 2 million yen/company/year

6. Research funds (industry-academia collaborative research, contract research, clinical trials) provided by a company and for-profit organization.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 10 million yen/company/year, (3) equal to or more than 20 million yen/company/year.

7. Donations for scholarships and incentives offered by a company and for-profit organization.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

8. Employed by organizations or departments sponsored by companies, with donations equal to or more than 1 million yen.

9. Other remunerations (e.g., travel grant, not directly related to research, gifts).

Classification of amount: (1) equal to or more than 50 000 yen, (2) equal to or more than 200 000 yen, (3) equal to or more than 200 000 yen.

Spouses or First-Degree Relatives of Participants, Those Who Share Income or Property Interests With Participants

1. Presence or absence of officers and advisors in companies and for-profit organizations and the amounts of their remunerations.

Classification of pension amounts: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

2. Ownership of stocks and profits derived from the stocks (profits for the previous year presented in this format).

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

3. Royalty payments for patents by companies and for-profit organizations.

Classification of amount: (1) equal to or more than 1 million yen/company/year, (2) equal to or more than 5 million yen/company/year, (3) equal to or more than 10 million yen/company/year.

Organizations or departments that participants belong to

1. Research funds (industry-academia collaborative research, contract research, clinical trials) provided by a company and for-profit organization.

Classification of amount: (1) equal to or more than 10 million yen/company/year, (2) equal to or more than 20 million yen/company/year, (3) equal to or more than 40 million yen/company/year.

2. Donations for scholarships and incentives offered by a company and for-profit organization.

Classification of amount: (1) equal to or more than 2 million yen/company/year, (2) equal to or more than 10 million yen/company/year, (3) equal to or more than 20 million yen/company/year.

Criteria for exclusion from the committee: Members of the guideline drafting committee, their spouses, first-degree relatives, or those who share income or property interests if they fall under any of the following:

1. Incomes of the officers and advisors of companies and for-profit organizations equal to or exceeding 1 million yen/company/year.

2. Ownership of stocks and profits generated from the stocks equal to or exceeding 5% of total stocks of the company or 1 million yen/company/year.

3. Receipt of patent royalties from companies and for-profit organizations equal to or exceeding 1 million yen per company per year.

4. Employed by organizations or departments sponsored by companies and for-profit organizations.

Criteria That Should Be Met By the Chairperson of the Guideline Drafting Committee

Both individual and organizational COI are classified into Category (1) or below.

Criteria That Should Be Met By the Members of the Guideline Supervisory and Drafting Committees

Both individual and organizational COI are classified into Category (2) or below. However, the number of persons in Category (2) shall not exceed half of the guideline drafting committee.

List of the COI

Minoru HASEGAWA (member of the guideline supervisory committee), financial COI, Maruho Co. Ltd. (Category (2) or below), Ono Pharmaceutical Co. Ltd. (Category (2) or below).

Manabu FUJIMOTO (member of the guideline supervisory committee), financial COI, Maruho Co. Ltd. (Category (2) or below).

Takeo MAEKAWA (member of the guideline drafting committee), financial COI, Ono Pharmaceutical Co. Ltd. (Category (2) or below), Sun Pharma Japan Ltd. (Category (2) or below), Taiho Pharmaceutical Co. Ltd. (Category (2) or below), Maruho Co. Ltd. (Category (2) or below), Mitsubishi Tanabe Pharma Corporation (Category (2) or below), Eisai Co. Ltd. (Category (2) or below), Leo Pharma K.K. (Category (2) or below).

Takaaki ITO (member of the guideline drafting committee), financial COI, Sun Pharma Japan Ltd. (Category (2) or below).

Takamitsu TANAKA (member of the guideline drafting committee), financial COI, Maruho Co. Ltd. (Category (2) or below), Sun

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Non-Financial COI

Takafumi Kadono is the Editor-in-Chief of the *Journal of Dermatology* and is acknowledged in this article. Takafumi Kadono is excluded from editorial decision-making related to the acceptance and publication of this article.

Minoru HASEGAWA is an Editorial Board member of the *Journal of Dermatology* and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

Mari Kishibe and Hideki Fujita are the Editorial Board Members of the *Journal of Dermatology* and are acknowledged in this article. Mari Kishibe and Hideki Fujita are excluded from editorial decision-making related to the acceptance and publication of this article.