Recommendations for the diagnosis and treatment of chronic venous disease

Slovenian Society of Vascular Diseases at SZD, Working group for chronic venous insufficiency: Nada Kecelj Leskovec,[1] Matija Kozak,[2] Ana Slana,[1] Katarina Šmuc Berger,[3] Andrej Šikovec,[4] Matej Makovec,[4] Aleš Blinc,[2] Ivan Žuran,[5] Tanja Planinšek Ručigaj[1]

[1] *Department of Dermatovenereology, University Medical Centre Ljubljana, Ljubljana*

[2] *Department of Vascular Diseases, Division of Internal Medicine, University Medical Centre Ljubljana, Ljubljana*

[3] *Dermatology clinic, General hospital Izola, Izola*

[4] *Surgical division, General hospital Novo mesto, Novo mesto*

[5] *Non-Surgical Medical Division, General hospital Celje, Celje*

Correspondence:
Matija Kozak, e: matija.kozak@kclj.si

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Abstract

Clinical manifestations of chronic superficial venous insufficiency are described, followed by recommendations for diagnostic evaluation and various treatment possibilities.

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1. Definition of chronic venous disease and insufficiency

Chronic venous disease (CVD) involves all stages of the disease from teleangiectasis, varicose veins and edema to skin ulcerations, Chronic venous insufficiency (CVI) refers to an advanced stage of the disease characterized by persistent swelling and presence of skin changes with ulcer formation (1). CVD is clinically defined as a group of symptoms and signs resulting from increased pressure in superficial and/or deep veins of the low extremities. Symptoms of CVD may include feeling of heaviness in the legs, dull ache, itching and fatigue of the legs, night cramps and restless legs. CVD is characterized by the following clinical signs: reticular veins or varicose veins, edema and skin changes, such as hyperpigmentation, lipodermatosclerosis, hypostatic dermatitis and venous leg ulcer (1).

Elevated venous pressure is most commonly due to malfunctioning of venous valves which fail to prevent the blood from flowing backwards (reflux); and less frequently to the narrowing or occlusion of the proximal vein. In patients with incompetent venous valves, calf muscle pump fails to lower venous pressure in the legs adequately during walking. Most patients present with primary venous insufficiency of unknown etiology (1). Secondary venous valve failure, which leads to formation of varicose veins, occurs in acute lower extremity deep venous thrombosis, failure of recanalization of thrombosed iliac veins or in post-thrombotic syndrome. Congenital insufficiency occurs in patients with congenital dysplasia of the venous system (1).

CVD is initially manifested by disturbance in venous macrocirculation,

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affecting superficial (extrafascial) and/or deep (intrafascial) veins. Elevated intravenous pressure soon affects microcirculation, leading to impaired blood flow regulation, inflammation activation, leakage of plasma proteins into the extracellular space, interstitial edema, hypoxia and damage to the adjacent tissues, with the resulting legulceration of the calf skin, referred to as venous leg ulcer (2).

2. Classification of CVD

Several systems of CVD classification have been developed. The most simple one is Widmer's classification based on morphological characteristics (3). A more detailed CEAP scale includes clinical (C) etiologic (E) anatomic (A) andpathophysiologic (P) aspects of the disease (4). Clinical classification takes into account clinical signs of CVD and comprises seven groups (Table 1). A subscript letter added to C indicates the presence of symptoms (s) or absence of symptoms (a).

The etiology is classified as either congenital (Ec), primary (Ep) or secondary (Es). Anatomic classification is based on the involvement of superficial (As), deep (Ad), or perforator veins (Ap) (Table 2). The superificial and deep venous systems communicate via the saphenofemoral and saphenopopliteal junctions and the perforating veins that pass through the fascia. In addition to comitant veins that accompany calf arteries, the deep calf venous system comprises muscle sinusoids that drain soleal and gastrocnemius muscles below the knee.

The underlying pathophysiology is related to either reflux (r), obstruction (o), or both (r + o)

While CEAP classification describes the clinical grade of the disease, Venous Clinical Severity Score (VCSS) (Table 2) assesses presence/absence of clinical manifestations of the disease, and has proved more useful in the daily clinical practice (5).

3. Epidemiology

The prevalence of CVD of the lower extremities ranges between 10 to 50 % for adult men and 50 to 60 % for adult women. Clinical signs of varicose veins are present in 10 to 33 % of adult women and in 10 to 20 % of adult men (1,6). Advanced forms of CVD characterized by edema and trophic skin changes, eczema and hyperpigmentation are encountered in 3 to 11 % of the population. Active venous ulceration affects 0.3 % of adults in the economically developed countries. The prevalence of healed and active ulcers in the general adult population and the elderly is 1 % and 3 %, respectively. One-half of ulcers heal within 4 to 6 months, yet 20 % fail to heal after 2 years, and 8 % remain unhealed after 5 years (7). Similar figures have been reported for the Slovene population (8). As many as 85 % of people with varicose veins have a family history of varicose veins.The prevalence of CVD increases with the

Table 1: CEAP clinical classification

C 0 – no visible or palpable varicose veins
C 1 – telangectasia or reticular veins
C 2 – varicose veins
C 3 – edema
C 4a – acute skin changes (hyperpigmentation, dermatitis)
C 4d – chronic skin changes (white atrophy, lipodermatosclerosis)
C 5 – skin changes described for class 4, and healed venous leg ulcer
C 6 – above described skin changes and active venous leg ulcer

Table 2: Classification of chronic venous disease by the disease extent.

	No signs: 0	Mild: 1	Moderate; 2	Severe: 3
Pain	absent	occasional; no effect on daily life activities	daily; no effect on daily life activities	daily, affects daily life activities
Varicose veins	absent	*corona phlebectatica, isolated varicose branches*	varicose veins of the calf or thigh	varicose veins of the calf and thigh
Edema	absent	around the ankle	lower half of the calf	calf
Skin pigmentation	absent	around the ankle	lower third of the calf	calf
Inflammation	absent	around the ankle	lower third of the calf	calf
Induration	absent	around the ankle	lower third of the calf	calf
Venus leg ulcer				
Duration (months)	absent	<3	3–12	>12
Size (circumference in cm)	absent	<2	2–6	>6

increase in the number of births. There is a positive correlation between body weight and CVD (1.2)

4. Diagnosis

4.1. History taking and physical examination

Patient assessment includes: family history with a focus on the occurrence of CVD in immediate family members because of undoubtedly confirmed familiar predisposition for CVD (1), personal medical history (the length of time he/she has had varicose veins, swelling, pain, cramps, heavy, tired or restless legs, general health status, known allergies, drugs taken on a regular or occasional basis), past medical history (known disorders of peripheral nerves, possible history of venous thrombosis or thrombophlebitis (TP), trauma, previous management of varicose veins, presence of other metabolic and systemic diseases, number of births, use of hormonal contraceptives or hormonal replacement therapy in women, and social history (occupation, lifestyles). A targeted physical examination focuses on the presence of varicose veins, *corona phlebectatica*, skin color, edema, clinical signs of infection, presence of palpable pedal pulses, capillary filling, skin temperature and foot arche type. Venous ulceration most frequently occurs in the lower third of the calf above the malleolus. The ulcers are usually shallow with adjacent skin changes, including erythema, hyperpigmentation, lipodermatosclerosis an white atrophy (1).

4.2. Basic non-invasive diagnostic procedures

The purpose of non-invasive diagnostic procedures is to confirm the diagnosis of CVD, perform hemodynamic measurements and determine whether CVD is due to obstruction or reflux

in a venous segment (1). Primarily the following three methods are used:

1. venous reflux measurement using a handheld Doppler device;
2. venous ultrasound examination;
3. venous plethysmoghraphy.

4.2.1. Venous reflux evaluation using a handheld doppler device

The investigation is done in the standing position. A handheld doppler probe is placed over the saphenofemoral junction (in the groin), or over the saphenopopliteal junction (in thepoliteal fossa). Calf squeezing forces blood in the vein up to the heart, and releasing the vein allows the blood to flow back

In the case of incompetent vein valves this reverse blood flow persists for more than 0.5 s after the release of calf compression (1). This test has a 92–93 % sensitivity for confirming retrograde venous flow, but its specificity is relatively low (54–74 %) because of high rates of false positive results (9). Therefore, the use of venous reflux assessment with a handheld doppler probe is limited to screening in mild cases of CVD.

4.2.2. Venous ultrasound examination

Venous ultrasonography is a non-invasive diagnostic modality for evaluating venous diseases of the lower extremities. Ultrasound of the calf veins is done with the patient standing or sitting with the leg hanging down. The examination provides a gray-scale (*B-mode*) image of a two-dimensional cross-section of tissue with a simlutaneous color image of blood flow in the vessels (color doppler). In a selected venous segment, blood flow velocity and direction can be determined using pulsed-wave doppler ultrasound. Compressibility of veins and the presence of reflux in the superficial and deep venous systems are evaluated. Retrograde venous flow is produced by the Valsalva maneuver or by a distal muscle squeeze. Reflux at the saphenofemoral junction is best evaluated using the Valsalva maneuver, while a quick squeeze of the leg distal to the examination site is recommended for assessing distal venous flow. Borderline duration of retrograde blood flow is 500 ms for the saphenous, tibial, perforating and deep veins, and 1s for the femoral and popliteal veins. A perforator vein is considered pathologic when retrograde venous flow persists for more than 500 ms and it is more than 3.5 mm in diameter, or when it is located underneath an active or healed ulcer (9,10). Compared to phlebography the sensitivity and specificity of ultrasonography for determining retrograde venous flow at the saphenofemoral junction is 95 % and 100 %, respectively. The sensitivity and specificity of ultrasound for assessing reflux in the perforating calf veins was reported to be 80–88 % and 75 %, respectively in comparison with phlebography and detection of retrograde venous flow during surgery (11). In addition, ultrasonography is used to detect TP in superficial veins, or to demonstrate venous thrombosis or congenital malformations of the deep venous system. The disadvantage of ultrasound examination is that it is time-consuming and depending on the skill and experience of the examiner. The examination is recommended in all patients with advanced CVD or recurrence after treatment, and in the first place for planning potential interventions (9).

4.2.3. Venous plethysmography

Plethysmography is based on the detection of venous volume changes in the lower limb and therefore helps assess dynamics of venous flow in the leg. The method is rarely used in clinical practice because of its low sensitivity and specificity rates. It can be used, however, after ultrasound has failed to assess the disease (10).

4.3. Diagnostic x-ray and magnetic resonance imaging

Descending venography is a gold standard in the diagnosis of venous reflux flow in the lower extremities, yet it has low sensitivity for detecting reflux below the knee (11,12). Ascending venography commonly used for the evaluation of the deep venous system is not sensitive enough for a reliable assessment of retrograde venous flow in the perforating calf veins (11). In clinical practice, disease evaluation by x-ray, MR and CT venography is used in selected cases of complex anatomy and pathology of the deep venous system difficult to visualize on ultrasound, or in patients planned for surgery of the deep venous system (1,12) It is reasonable to use these examinations in the evaluation of pelvic veins, venous malformations and in invasive intravascular procedures.

Recommendation	IIa C
It is reasonable to use screening with handheld Doppler probe in patients with mild forms of the disease manifested by telangiectasias and venectasias only.	

Recommendation	I A
Varicose veins are evaluated by ultrasound examination of the superficial and deep venous system.	

Recommendation	IIa C
The use of x-ray contrast venography, MR and CT venography is reserved for a small number of selected patients with anatomic venous malformations and for patients planned for surgery of the deep venous system.	

5. Treatment

Conservative therapy of CVD includes:

1. external compression therapy,
2. veno-active medication; and special treatment of two important complications of CVD, i.e.
3. TP and
4. venous leg ulceration.

5.1. External compression therapy

External compression includes the use of elastic and inelastic pressure garments that apply pressure to the limb and thereby treat and prevent CVD. The mechanisms behind external compression are not entirely clear, yet it has been shown that applying pressure to calf muscles elevates interstitial hydrostatic pressure, lowers pressure in superficial leg veins and improves venous return, thereby reducing venous hypertension, the basic pathophysiologic mechanism in CVD (13). External compression therapy is the mainstay of conservative management of CVD,

Table 3: Compression classes of medical compression stockings – French and German standards.

Class	Compression at the ankle (mmHg)	
	German standard	French standard
Class I	18.4–21.2	10–15
Class II	25.1–32.1	16–20
Class III	36.4–46.5	21–36
Class IV	>59	>36

and a measure taken to support other treatment options (14). In CVD patients with concomitant peripheral arterial disease, the use of external compression should be avoided when the ankle-brachial pressure index is less than 0.8 (15). Patients with an an index of less than 0.8, and patients with diabetes treated by external compression need regular follow-up examinations (16).

The purpose of external compression to the limb is to neutralize the pathologically elevated pressure within the veins of the lower extremities. During ambulation, compression applied to the calf surface by compression garments changes along with the changes in the calf circumference induced by leg muscle contraction, which increases the effect of muscle pump in patients with incompetent venous valves. The difference between external pressure applied to the leg at rest and that during ambulation depends primarily on the type of compression device. Great differences in pressures occur with short-stretch and non-stretch materials that expand to less than 100 % of their original length (passive intermittent compression). Small differences between pressures occur with long-stretch materials that stretch to more than 100 % of their orinignal length (constant active compression). Long-stretch fabrics exert high resting pressures and should be removed before going to bed because they reduce arterial circulation in the leg. Therefore, inelastic or short-stretch materials are used for compression that is maintained for several days (14).

For external compression long-stretch bandages and compression stockings are used. These are elastic devices and should be removed before going to bed at night. Short-stretch inelastic bandages, however, may stay on the leg for several days. Selection of appropriate fabrics and correct application of compression devices are of utmost importance for the efficacy of compression therapy. The form of external compression therapy is prescribed by a doctor. Patients apply long-stretch bandages or medical compression stockings on their own or with the help of family members. Inelastic short-stretch bandages are always applied by specially trained healthcare providers (14).

Compression bandages and medical compression stockings are used for compression therapy of venous leg ulcers following surgery or endovenous treatment. Patients with mild forms of CVD (CEAP 1–3) more frequently use medical compression stockings that are easier to put on (14).

If correctly applied, medical compression stockings exert graduated compression with the highest (standardized) pressure at the ankle, which is then gradually reduced up the leg, i.e. to 70 % at the calf and 40 % at the thigh.On the basis of standards applied by the German manufacturers of Medical Compression Hosiery, compression stockings RAL-GZ 387 fall into four classes (Table 3) (14,17). The length of compression stockings can vary from below the knee to up the groin. The use of knee-length stockings is reasonable in most patients, especially during the summer months (10).

The use of ordinary anti-embolism stockings that apply graduated pressure of 18 mmHg at the ankle and 8 mmHg at the thigh is recommended in healthy individuals with a positive family history of CVD. As patients at incipient stages of CVD are not strongly motivated to use compression garments and as there is a lack of convincing evidence on the effectiveness of compression therapy in preventing disease progresssion at early stages (18), compression therapy is not recommended in these cases, or the decision on whether to start the therapy is taken individually.

Treatment by external compression is reasonable in advanced forms of the disease.

Compression therapy applying pressures of 20 to 30 mmHg at the ankle (class II compression stockings) is recommended in patients with symptomatic varicose veins, especially if associated with constant ankle or calf swelling (mild CVD), who are not planned for invasive procedures (1).

Compression therapy is the first treatment option for venous leg ulcers because it improves symptoms and promotes ulcer healing. Compression can be applied using multilayer compression systems (adhesive, non-adhesive and self-adhesive), long- stretch bandages and compression stockings for ulcerations requiring higher degrees of compression. Multilayer short-stretch compression systems can be worn for several days (day and night) until the next visit by a district nurse. Long-stretch bandages and compression stockings for ulcers are worn only during the day. Cooperation of the patients and their family members is most important to the success of thie therapy. The choice of the most appropriate form of compression therapy depends on the patient‘s clinical status, as well as on the patient, family or nurse cooperation (1). Once the venous ulcer has healed, the use of constant compression therapy is recommended with the aim of reducing the risk of venous leg ulcer recurrence (15,16,19).

Recommendation	**IIa B**
In patients with symptomatic varicose veins and leg edema, therapy applying compression of 20–30 mmHg at the ankle is recommended (class II compression stockings).	

Recommendation	**I A**
Compression is the first-line therapy in patients with venous leg ulceration.	

Recommendation	**IIa C**
The choice of the most appropriate compression therapy depends on the patient‘s clinical status, as well as on the doctor‘s experience and the level of cooperation with the patient, his/her family and the nurse.	

Recommendation	**IIa B**
Multilayer compression systems that apply high intermittent compression to the leg should be used for the treatment of venous leg ulcers on condition that services of a trained district nurse are provided.	

Recommendation	**IIa B**
Compression therapy is used as an adjunct treatment following superficial vein ablation to prevent venous leg ulcer recurrence.	

5.2. Treatment of CVD with venoactive drugs

Venoactive drugs are a heterogenous group of medicinal products used to reduce symtpoms and signs of CVD, including pain, discomfort and swelling (1). On the basis of their composition they are divided into four groups: benzopyrones, saponins, other plant extracts and synthetic drugs (1,20). Venoactive agents available on the Slovenian market include: micronised purified flavonoid fraction (MPFF) (diosmin, hesperidin) from the family of benzopyrones, and escin from the saponin group. Another agent used for CVD treatment is pentoxyfylline though it does not belong to the group of venoactive drugs.

Venoactive drugs increase venous tone, improve capillary hyperpermeability, enhance lymph flow and improve rheological properties of blood (1,21). Moreover, MPFF inhibits leukocyte adhesion and migration to and transmigration of leukocytes into the venous wall (22).

Meta-analysis of the effects of venoactive drugs on leg edema showed that micronized flavonoids reduce swelling (23) and, when used in combination with compression therapy, improve symptoms in CVD patients with stage C4 disease (24). It has been shown that they improve healing of ulcers (25). Similarly, escin improves subjective symptoms and reduces swelling (26). Pentoxyfilline used as an adjunct to treatment of venous leg ulcers increases the chances of healing 2.25 fold. It can be given to patients in whom compression therapy is contraindicated (27).

The use of venoactive drugs is recommended in patients with signs and symptoms of CVD as adjuvant therapy to other treatment options. However, additional quality studies using appropriate methodology are required to further support the use of these agents (20,22,25,28).

Recommendation	**IIa B**
In C2-C6 stage disease, venoactive therapy is recommended as an adjunct to standard compression therapy. (IIB for MPFF, IIb B for escin)	

Recommendation	**IIb B**
The use of pentoxyfilline in combination with compression therapy is recommended in patients with venous leg ulcers, including those with mixed arteriovenous ulcers in whom compression therapy is contraindicated.	

Recommenation	**IIa B**
Treatment with venoactive drugs is recommended if other treatment options have failed to produce the desired effects (wound healing or improvement of symptoms).	

5.3. Treatment of thrombophlebitis

Thrombophlebitis (TP) is a sterile acute inflammation of the venous wall and adjacent tissue, accompanied by thrombus formation leading to incomplete or complete obstruction of the superficial vein. Congenital and acquired risk factors involved in the development of TP include: varicose veins, various inherited thrombophilic states, malignancy, obesity, impaired mobility, states following trauma and surgery, hormonal treatment, pregnancy, venous catheters, some

drugs and infections. When TP occurs in a varicose vein, injury to the vein leads to inflammatory reaction. Venous thrombosis represents a secondary process, most likely accelerated by venous flow changes or occlusion.TP that arises in a healthy vein is usually due to a blood clotting disorder (1).

It has been shown that 25 % of patients diagnosed with TP had concomitant venous thrombosis or pulmonary embolism, and that in 10 % of the patients, these complications occurred within the following 3 months (29). Clinically manifest venous thrombosis occurs less frequently, but symptomatic pulmonary embolism was diagnosed in as many as 13 % of patients with TP (29,30).

TP is a common disease affecting 2 to 11 % of the population (31). The disease has a female predilection; the mean patient age is 60 years; the patients are obese and have varicose veins (29, 30).

Symptoms of TP include local swelling, redness, warmth and pain that follow the course of the involved superficial vein. Once the acute inflammation settles, skin hyperpigmentation and induration may remain over the affected vein, which often becomes blocked or incompetent (1).

The diagnosis is made on clinical grounds; but additional investigations (especially ultrasound) are used in doubtful cases or to determine the extent of TP (31). Ultrasound examination should always be done in TP patients with suspected venous thrombosis, in patients with TP involving the course of the great saphenous or small saphenous veins, or in patients who show progression of TP symptoms despite therapy. A few months after TP, repeated ultrasound is done to assess chronic venous insufficiency. Timely treatment of chronic venous inufficiency most likely prevents important recurrent episodes of TP.

Spontaneous TP that arises in an unaffected vein, should be distinguished from TP occurring in a varicose vein. Factors triggering the disease should be identified in these patients. A detailed history and physical examination should be aimed at discovering possible symptoms and signs of malignancy or thrombophilia (32).

The type of TP treatment depends on the extent and location of the disease. All patients are given symptomatic treatment that includes compression therapy in combination with normal physical activity, especially walking. There is a lack of evidence for the effectiveness of local therapy with cold packs or topical application of heparin cream or gel. Local cooling has been shown to relieve symptoms of nonbacterial local inflammation, while warmth usually alleviates pain (10). Some patients (see recommendations) need anticoagulant therapy. Several treatment options have been proposed, the most widely supported being treatment with fondaparinux (a 45-day course of s.c. Arixtra 2.5 mg). In patients with concomitant diseases (e.g. renal impairment), or in pregnant women, in whom the use of this drug is contraindicated, treatment with a low-molecular-weight heparin is a sensible option (32).

Recommendation	IIa A
Patients with clinical signs of extensive TP of lower extremities should have an ultrasound examination to determine thrombus size and exclude possible co-existing venous thrombosis.	

Recommendation **IIa C**

In patients with TP compression therapy and exercise are recommended.

Recommendation **I B**

TP associated with venous thrombosis or pulmonary embolism is treated in accordance with the guidelines for the treatment of venous thromboembolism; the treatment is the same as for TP located at a distance of less than 3 cm from the saphenofemoral or saphenopoliteal junctions.

Recommendation **I B**

All patients with symptomatic TP involving the small or the great saphenous vein, longer than 5 cm and located at a distance of more than 3 cm from the saphenofemoral or saphenopopliteal junctions are prescribed subcutanous fondaparinux 2.5 mg/24h for 45 days. If the therapy is contraindicated, low-molecular-weight heparin prophylaxis is used.

Recommendation **IIa B**

Patients with TP less than 5 cm in length need no anticoagulant therapy. Yet anticoagulant treatment is instituted once the disease has progressed to the level (determined on clinical and ultrasonical grounds) that meets all the previously described requirements for the use of anticoagulant therapy.

Recommendation **IIa C**

In TP patients without involvement of great superficial veins (small and great saphenous veins) anticoagulant therapy is not required.

5.4. Treatment of venous leg ulceration

It is estimated that among chronic leg ulcers that by definition remain unhealed for at least 4 weeks, there are 60–80 % venous ulcers, 10–30 % ulcers associated with advanced peripheral arterial disease and 10–20 % mixed ulcers occuring in patients with co-existent CVD and peripheral arterial disease (1,34). Neuropathic ulcers in diabetes, which occur more frequently at pressure points on the plantar surface of the foot than on the leg, as well as ulcers accompanying systemic tissue disorders and ulcers associated with malignant neoplasm should also be considered in the differential diagnosis. Patients with suspected venous leg ulceration should undergo ultrasound examination to evaluate their venous disease. In addition, blood flow measurement in the leg arteries using doppler ultrasound and calculation of brachial-ankle pressure index are indicated in these patients (35). Routine cultures for bacteria are not needed, yet swab samples should be taken from ulcers with marked signs of local inflammation, including redness around the ulcer, increased pain, increased purulent exudate, foul odor and ulcer bed covered with a fibrine layer, and in patients with systemic inflammation signs. Patients with venous leg ulcers are as a rule managed on an outpatient basis; the care is based on local wound treatment and application of compression therapy. Cooperation with district nurses is very important. Between dressing changes, cleaning of the ulcer is recommended using irrigation with

lukewarm potable tap water or saline solution. Stasis dermatitis around the ulcer is treated by application of topical steroid cream. Once ertyhema has cleared application of neutral ointments is indicated (36). Ulcer is covered with non-adhesive dressing that does no stick to the wound or its environment, and produces no pain during application and removal, and is affordable for the patient. There is no compelling evidence that any one dressing type is more effective than any other in enhancing ulcer healing; yet clinical experience has confirmed that selecting the most appropriate dressings can improve the patient's quality of life. The choice depends on the presence of granulation, necrotic or fibrinour layers in the ulcer bed and on the amount of exudate (36). Application of hydrogels is indicated in wounds with ulcer bed covered with necrotic or fibrinous layers, and with only small amounts of exudate. Alginate dressings or other highly absorbent wound care products are used when there is abundant exudate. The use of polyurethane foam, hydrocolloid dressings or microfibers is recommended in ulcers with granulation tissue, minimal fibrinous tissue and small amounts of exudate. Dry and shallow sores are covered with transparent films (36). Allergic reactions to wound dressings are rare.

Compression therapy is the mainstay of treatment promoting venous leg ulcer healing in CVD. It is not indicated in patients with peripheral arterial disease with a brachial-ankle pressure index of < 0.8. An angiologist should be consulted regarding the use of adapted compression therapy in patients with brachial-ankle pressure index of 0.5–0.8 (14).

Treatment with **venoactive drugs**, especially with micronised diosmin, has proved beneficial in patients with venous leg ulcers (28).

After ulcer healing has been accomplished, long-term compression therapy – with or without ablation of superficial vein – is necessary to prevent recurrence (34).

Recommendation	**IIb C**
The patient with a suspected venous leg ulcer should be seen by a doctor experienced in identifying causes of the disease.	

Recommendation	**IIa B**
Patients with venous leg ulcer should have ultrasound examination to evaluate venous disease and doppler ultrasound measurement of blood flow in the leg arteries to calculate brachial-ankle pressure index.	

Recommendation	**I A**
Conpression therapy is recommended in patients with venous leg ulcer and brachial-ankle pressure index of > 0.8.	

Recommendation	**I B**
In addition to compression therapy, ablation of incompetent superficial vein is recommended to facilitate ulcer healing and reduce ulcer recurrence.	

6. Treatment of varicose veins

Goals of treatment:

- excluding varicose veins from venous blood circulation;
- preventing and treating complications of CVD;
- improving symptoms and the patient's quality of life;

- improving venous function, and
- esthetic improvement.

Endovenous treatment of varicose veins

1. Chemical ablation (sclerotherapy)
2. Laser or radiofrequency ablation

6.1. Sclerotherapy

Sclerotherapy involves injecting a sclerosing agent into the varicose vein, which causes vascular spasm, imflammatory reaction and scarring of the vessel wall. Ideally, the entire vein lumen is filled with scar tissue, which leads to complete tissue remodelling in the incompetent varicose vein (37).

Sclerotherapy with sclerosant liquid or foam is a safe and effective option for treating telangiectases, and reticular and subcutaneous varicose veins (38). The success rate of liquid sclerotherapy for the treatment of telangiectases and reticular varicose veins is 90 % (39). Similar results are achieved with sclerotherapy performed with foam, if low sclerosant concentrations are used to prepare a larger volume of foam (40).

In patients with large varicose veins, foam sclerotherapy gives better results than sclerotherapy using liquid sclerosants. The outcome of vein closure depends on the size of the targeted vein, the concentration of the sclerosing agent, the volume of the injected foam and teh selected sclerotherapy technique (intravenous or long catheter-directed) (41).Foam sclerotherapy is only 30 % less effective than classical surgical procedures or endovenous laser or radiofrequency ablation, yet there is no differences between the techniques regarding the improvement of symptoms and quality of life. There is no documented evidence that the procedure is more effective and associated with less side effects when performed with the leg elevated, or if the ultrasound probe is pressed against the trunk orifice (42).

Foam sclerotherapy promotes ulcer healing and is therefore indicated for treating recurrent varicose veins, accessory veins, venous malformations, and feeding varicose veins close to the ulcer. Repeated sclerotherapy is recommended in partially recanalized veins because it improves mid-term treatment outcome (43).

Therapy with medical compression stockings or bandages improves the outcome of sclerotherapy of telangiectases and reduces the risk of hyperpigmentation (4). The efficacy of sclerotherapy is further increased by the use of local eccentric compression, which markedly elevates pressure over the sclerotherapy site (45).

Recommendation	**I A**
The use of liquid sclerotherapy in recommended for the treatment of telangiectases and reticular varicose veins (C1) (recommendation grade I A). Foam sclerotherapy is used as an alternative treatment (recommendation grade II a B)	

Recommendation	**I A**
Foam sclerotherapy is recommended for treatment of large varicose veins (C2) (recommendation grade I A), venous malformations (recommendation grade II a B), recurrent, accessory or perforating varicose veins (recommendation grade II a C).	

Recommendation	**I B**
Repeated sclerotherapy is indicated in partially recanalized veins.	

Recommendation I B

Sclerotherapy of feeding varicose veins near the ulcer is recommended to promote wound healing.

Absolute contraindications to sclerotherapy include: known allergy to the sclerosant agent, acute venous thrombosis or pulmonary embolism, local infection at the site of sclerotherapy or systemic infection, prolonged immobilization or bedridden and wheelchair-bound states. Symptomatic right-to-left shunting (patent foramen ovale) is also a contraindication for foam sclerotherapy (46).

Relative contraindications to these procedures include: pregnancy, breast feeding, advanced peripheral arterial disease, poor health condition, history of allergies, hypercoagulable states (e.g. thrombophilia, active cancer) and acute TP. Foam sclerotherapy is contraindicated in patients with neurologic disorders and patients who developed migraine after previous sclerotherapies (47).

Anticoagulant treatment per se is not a contraindication for sclerotherapy (48-50).

Allergic reactions to sclerosing agents are rare. Hyperpigmentation, necrosis, superficial TP or phlebitis may occur after Sclerotherapy, while venous thrombosis is rare (14). Nerve injury associated with sclerotherapy is a very rare event (51).

6.2. Endovenous thermal ablation (EVTA)

Endovenous thermal ablation is a catheter-guided, ultrasound-controlled procedure, based on heating the vein wall to produce thermal injury in the form of denaturation of proteins and inflammation, resulting in fibrosis and occlusion of the treated vein (52). **Endovenous laser ablation (EVLA) and radiofrequency ablation (RFA)** are the most thoroughly documented vein ablation procedures (10,53-55), and can be performed in outpatient clinics under local tumescent anesthesia. Under ultrasound guidance a RF catheter or a laser fiber is advanced percutaneously into the vein and positioned accurately at a desired location within the vein. These patients report less postoperative pain and a faster return to work than patients undergoing classical surgery (56).

Indications for treatment with EVTA include: incompetent subfascial segment of the superficial vein (57), at least 5 cm long and 3 mm wide, and/or incompetent perforating veins and/or venous malformations. Incompetent perforating veins are mostly treated with EVLT because the active fiber tip of the catheter used in RF ablation is only 5 cm long (58).

Absolute contraindications include: acute venous thromboembolism, acute TP, local or systemic infection, prolonged immobilization, deep vein occlusion. In addition, the procedure is contraindicated in patients prone to thromboembolism (hypercoaguable states, active cancer) and if the target vein is a collateral vein. Relative contraindications include: pregnancy, breast feeding, advanced peripheral arterial disease, impaired mobility, poor general health, marked inclination to allergies or allergy to a local anesthetic (59). For technical reasons, the therapy is contraindicated in TP-related vein occlusion that precludes catheter insertion, in too tortuous veins (57) and in aneurysm-related changes of saphenofemoral junction (60).

Serious adverse effects of EVTA include nerve injuries, which occur in approximately 1–10 % of the procedures. Frequent mild complications of EVTA

include phlebitis, skin pigmentation, ecchymosis and pain, whereas skin burns are rare. The rate of venous thrombosis and pulmonary embolism is less than 0.1 %, and arteriovenous fistulas and stroke are even more rarely reported complications (61).

Both treatment modalities show short- and long-term efficacy in more than 90 % of patients (62-64). After the procedure, the patient is fitted with eccentric compression devices and compression bandages or stockings to reduce postoperative pain. Anticoagulant prophylaxis should be reserved for patients with increased risk for deep venous thrombosis (58).

Recommendation	I B
The use of endovenous thermal laser or radiofrequency ablation is recommended for treatment of incompetent saphenous vein, incompetent perforating veins and venous malformations.	

Recommendation	IIa B
Compression bandages or compression stockings are used to relieve pain after endovenous thermal ablation.	

6.3. Surgical treatment of varicose veins

Indications for surgical treatment of CVD include a broad spectrum of entities, including cosmetic aspect, pain, heaviness and fatigue of legs, history of superficial TP, bleeding from ruptured varicose veins, hyperpigmentation around the ankle, lipodermatosclerosis, white atrophy and active or healed venous ulceration.

Classical operative treatment of varicose veins involves removal of the great saphenous vein from the groin to the ankle level, segmental extraction with additional phlebectomies, ligation (high, medium, low) of the saphenous branch, additional sclerotherapies, ligation of the saphenous vein with additional phlebectomies, or phlebectomies alone.

The results of surgical treatment of CVD have improved recently, primarily as a result of advancement in classical operative techniques based on improved understanding of anatomy and pathophysiology of CVD, and thanks to the introduction of new minimally-invasive operative approaches (miniphlebectomy, vein removal by invagination) and the use of preoperative ultrasound that allows for accurate evaluation of the orifice of small saphenous vein and perforating veins of the leg.

The chance of recurrence 5 years after removal of the great saphenous vein is 6 %, whereas 5 years after ligation of the great saphenous vein re-operation was required in 21 % of the patients (65). Removal of the great saphenous vein to the knee level is therefore recommended in all patients undergoing classical surgery. Variable termination of the small saphenous vein into the deep vein needs to be evaluated by a preoperative ultrasound. Only its proximal and incompetent segment is removed (66).

Recommendation	IIa B
Surgical treatment of the great saphenous vein should involve high ligation of the saphenofemoral junction and reverse stripping of the great saphenous vein to the knee level.	

Recommendation	II a B
Operative treatment of the small saphenous vein should involve high ligation of the vein in the popliteal fossa, 3 to 5 cm from the saphenopopliteal junction and selective reverse stripping of its incompetent segment.	

Recommendation	II a B
Lateral superficial varicose veins are treated operatively with phlebectomies performed simultaneously with ablation or stripping of the saphenous veins.	

Recommendation	II a B
Postoperative compression therapy is recommended to reduce hematoma, swelling and pain after the operation.	

Recommendation	II C
Recommended treatment options for recurrent varicose veins include: ligation of the saphenous trunk, outpatient phlebectomies, sclerotherapy or endovenous laser ablation, selected depending on the etiology,origin, location and extent of the varicosity.	

6.4. A comparison of classical surgical techniques and EVTA

EVTA has the following advantages over classical surgery: it is performed in an outpatient setting under local tumescent anesthesia and is associated with less postoperative pain and faster recovery. Its disandvantage is that it is more expensive. The efficacy rates of both techniques at one year after the procedure are at equivalent (67), but several studies have reported better results with EVTA (56).

Perioperative costs were higher for RFA, yet the overall societal costs were lower because of the patient‘s faster return to work.Two years after the operation the efficacy rate was the same for both procedures (68).

A comparison of the two endovenous techniques showed that RFA was associated with less pain and subcutaneous hematomas (68). Higher long-term efficacy of RFA, however, has not been confirmed. All studies provide reliable data for a short postoperative period and safety, while reports on long-term results are less reliable.

Recommendation	I B
Endovenous thermal ablation is preferred over classical surgery because of shorter treatment, and less postoperative pain and morbidity.	

Surgical treatment of deep venous system, which involves internal valvuloplasty, external valvuloplasty (with synthetic cuffs or direct suture) and venous transposition or grafting, is reserved for selected patients and should be performed by specially trained surgeons in fully equipped medical centers.

Recommendation	III b C
Surgery to correct deep venous insufficiency is not performed in daily clinical setting and remains reserved for selected patients and specially trained surgeons in fully equipped medical centers.	

7. Evidence identification and evaluation

The recommendations take into account the results of studies conducted hitherto. Evaluation of these studies has been taken into consideration (Table 4).

Table 4: Evaluation of recommendations.

Recommendation grade	
Grade I	procedure or therapy is recommended
Grade II	opinion on the procedure or therapy is not entirely reliable; conflicting data
Grade II a	benefits are more likely – it is reasonable
Grade II b	benefits are questionable: no harm
Grade III	procedure or therapy is harmful
Strength of evidence	
A	numerous randomized studies or meta-analysis
B	one randomized study or several large-scale nonrandomized studies
C	opinion of experts or results of small-scale studies, data from registries

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