



# European Dermatology Forum

## S3-Guideline for Diagnostics and Treatment of Venous Leg Ulcers

Developed by the Guideline Subcommittee of the  
**European Dermatology Forum**

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## **EVIDENCE BASED (S3) GUIDELINES FOR DIAGNOSTICS AND TREATMENT OF VENOUS LEG ULCERS**

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## GENERAL

The need for European guidelines in dermatology is indicated by the ongoing development in European dermatology. The EDF, the EADV and the ESDR headed by the UEMS, also officially approved by the European Community, form the structure of pan European dermatology.

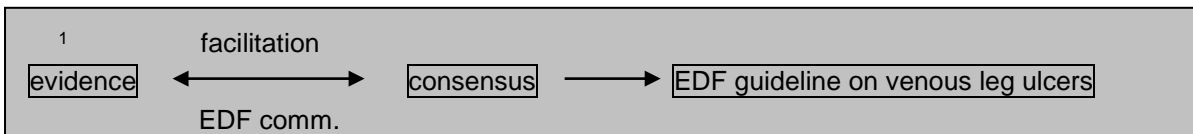
The European guidelines differ substantially from individual national guidelines. The main differences are:

No restrictions by different national regulations for EDF Guidelines

No restrictions imposed by local rules on drug distribution, reimbursement facilities, etc.

The diagnosis and the treatment of venous leg ulcers is an important item within all European dermatological departments. Although, this is not exclusive for this particular specialism, phlebology surgeons, physicians interested in vascular medicine and general practitioners also treat patients with venous leg ulcers. Nonetheless, the most difficult and complicated cases are treated by dermatologists.

Therefore, the European Dermatological Forum has decided to compile a European guideline on this subject. The process was as follows:



This EDF guideline replaces the EDF guideline venous leg ulcers 2006

## Introduction

This guideline on the management of venous leg ulcers was prepared by the guidelines committee of the European Dermatological Forum (EDF) and based on the already existing EDF guideline venous leg ulcers (2006). It presents evidence-based approach for treatment, identifying the strength of evidence available at the time of preparation of the guideline, and a brief overview of epidemiological aspects, diagnosis and investigation (level S3).

### Aim

This guideline is a document with recommendations and management instructions supporting the daily practice in which the optimum treatment (particularly healing and prevention of recurrences) of the patient is central. The guideline is based on the results of scientific research and contiguous opinions aimed at explicating good medical practice. The document is intended as a guideline for the everyday diagnostics and treatment of venous leg ulcers by dermatologists or other medical specialists.

### Problem description and initial questions

Questions regarding the diagnostics, the treatment, the follow-up treatment and the organization of care of venous leg ulcers were answered for the purpose of developing the guideline.

## Working group

The Commission on guidelines of the European Dermatological Federation (EDF) inaugurated the Chairman of the working group on wound healing during its annual meeting in January 2004.

This guideline is the first on wound healing and covers the subject of venous leg ulcers.

## Scientific basis

This guideline is based on the earlier guideline venous leg ulcer from 2006 and as much as possible on the proof provided in published scientific literature. Relevant publications were searched via systematic search in Medline, Cochrane and Cinahl databases from 1995 to 2012. Previously searched literature was used for the literature prior to 1995. Hereby, it must be remarked that evidence-based medicine started relatively late in Phlebology. This meant that much of the Anglo-Saxon literature was a repeat of the earlier efforts (at international meetings) in French, German, Swiss, Italian or Spanish literature.

In addition to the publications found via literature search, articles were also extracted from requested list of references. Publications that remained after the selection by the members of the working group are cited as the basis for the various conclusions. The selected publications were then assessed on the quality of the research and were graded for the strength of proof by the members of the working group. The classification that was used hereby is shown in Table I.

One may consider that European references, especially in German and French are underestimated as compared with those from North America due to the of lack of papers cited in PubMed / M/code in the field of phlebology.

The assessment of the various publications may be found in the different texts under the heading "**scientific basis**". The scientific proof is then briefly summarized in a **conclusion**. The most important literature including the **strength of proof** on which this conclusion was based is cited in the conclusion. Since evidence-based medical (EBM) publications are limited in medical journals in a field in which it is hard to recruit enough and comparable patients, no improvement in the treatment of leg ulcers could be achieved, especially with surgical techniques (think of paratibial fasciotomy, etc.). Therefore, the experience of experts is essential and the "recommendation" is a good way to present it (Level D).

For a recommendation, besides the scientific proof, often other aspects such as patients' choices, costs, availability (in various echelons) of organizational aspects are important. These aspects are mentioned under the heading "**other considerations**". The **recommendation** is the outcome of the available proof and other considerations.

Following this procedure increases the transparency of the guideline. It offers an opportunity for an efficient discussion during the meetings of the working group and also increases the clarity for the user of the guideline.

Table I: Classification of the literature according to the strength of proof

For articles concerning: intervention (prevention or therapy)

A1	Systematic reviews of at least several studies of A2-level, whereby the results of individual studies are consistent.
A2	Randomized comparative clinical study of good quality (randomized, double-blind controlled trials) of adequate size and consistency.

B Randomized clinical trials of moderate quality or inadequate size or other comparative study (not randomized, comparative cohort study, patient-control-study).

- C Non-comparative study.
- D Opinions of experts, for example, the members of the working group.

For articles concerning: diagnostics

A1 Study into the effects of diagnostics on the clinical outcomes in a prospectively followed well-defined patient group with a previously defined policy on the grounds of the to be investigated test results, or a decision study into the effects of the diagnostics on the clinical outcomes, whereby results of studies of A2-level are used as a basis and adequate consideration has been given to the mutual dependence of the diagnostic tests.

A2 Study in light of a reference test, whereby criteria have been defined beforehand for the investigation test and for a reference test, with a good description of the test and the studied clinical population; it must concern an adequately large series of consecutive patients and must make use of the pre-defined cut-off values and the results of the test and the 'golden standard' must have been assessed independently. In situations in which multiple, diagnostic tests play a role, in principle, a mutual dependence and the analysis should be adjusted to this, e.g. with logical regression.

B Comparison with a reference test, description of the investigated test and the population, but excluding the characteristics that are mentioned further in A.

- C Non-comparative study.
- D Opinions of the experts, for example, members of the working group.

Level of the conclusions

- 1 One systematic review (A1) of at least 2 independently conducted studies of levels A1 or A2.
- 2 At least 2 independently conducted studies of level B.
- 3 One study of level A2 or B or a study of level C.
- 4 Opinions of the experts, for example, the members of the working group.

**Legal significance of guidelines**

Guidelines are not legal regulations, but “evidence-based” insights and recommendations, which should be satisfied by the care providers in order to provide good quality care. Considering that these recommendations are mainly based on the “average patient”, the care providers may, if required, deviate from the recommendations on the basis of their professional autonomy. Deviation from the guideline is necessary if the situation of the patient requires it. Any deviation from the guideline should be based on arguments and should be accurately documented.

**Revision**

The client / responsible authority will determine at the latest in 2019 whether this guideline is still valid. If required, a new working group is inaugurated for the purpose of revising and updating the guideline. The guideline will become redundant if new developments make revisions mandatory.

# Guideline development standard operating Procedure of EDF

Step	Responsible	Task
1	EDF Guidelines Committee (EDF-GC)	Decision on topic of specific guideline
2	EDF Guidelines Committee	Inauguration of subcommittee for specific guidelines, nomination of EDF members (50 %)
3	EDF Guidelines Subcommittee (EDF-GSubC)	<b>Identification</b> of all existing guidelines for the specific guideline (active process: literature survey plus contact with Dermatological Societies)
4	EDF Guidelines Subcommittee	<b>Selection</b> of the guidelines with highest quality. Criteria for selection: 1.Availability of strength of evidence 2.Availability of strength of recommendation 3.Evidence of mechanics of literature review
5	EDF Guidelines Subcommittee	Identification/nomination of additional 50% EDF members for the EDF-GsubC from amongst the authors of the best guidelines
6	EDF Guidelines Subcommittee	Nomination of chairperson for EDF-GSubC from the GSubC members
7	Chairperson	<b>Consideration</b> of involvement of other disciplines and patients' organizations
8	EDF Guidelines Subcommittee	<b>Meeting</b> 1.To decide the author of the first draft and to discuss the present guidelines, their strengths and weaknesses 2. Six months later to discuss the draft (consensus conference)
9	Chairperson	<b>Circulation</b> of the guideline draft to National Dermatological Societies for comments
10	Guidelines Subcommittee	<b>Circulation</b> of final version for approval among members of the guideline subcommittee
11	Chairperson of Subcommittee	<b>Delivery</b> of final version to EDF guideline chairperson
12	EDF Guidelines Committee	Review and comment on guideline
13	EDF Guidelines Committee chairperson	<b>Sending</b> of guideline for official approval to UEMS (formal approval)
14	EDF secretary	<b>Distribution</b> of guideline for in advance information to EDF members and National Dermatological Societies
15	EDF	Publication 1.On EDF homepage 2. In European Journal of Dermatology, British Journal of Dermatology and Journal of Deutsche Dermatologische Gesellschaft



## Chapter 1 – Epidemiology, Etiology and Symptomatology

### 1.1 Epidemiology

A venous leg ulcer is a defect in pathologically altered tissue on the lower leg on the basis of chronic venous insufficiency (CVI). It is a symptoms and signs complex based on an inadequate venous return, which leads to a decompensation of the venous and the microcirculatory function. Chronic venous ulceration is the severest manifestation of this disorder<sup>1</sup>. A venous ulcer with no tendency to heal within 6 weeks to 3 months or that has not healed within a year after optimum phlebological therapy is designated as therapy resistant<sup>2</sup>. About three-quarters of all leg ulcers are generally considered to be mainly of venous origin<sup>3</sup>.

Epidemiological data is more difficult to interpret than expected at first sight because of methodological differences. It makes a big difference whether a whole population, a particular group of individuals in a certain region or a patient population is investigated. The manner of registration also influences the outcome. Even filled-out polls, polls filled out by an investigator, special questionnaires on the presence of ulcers and whether or not a physical examination was conducted all have a considerable influence on the results<sup>4</sup>. The most recent and convincing data came from the Bonn Vein Study<sup>5</sup> and from the group of Fowkes<sup>6</sup>.

**Table I: Key statistics on venous leg ulcer**

<b>Prevalence</b>			
	all ages	1,5 - 3%	1
	> 80 years	4 - 5%	2,7
	active ulcers	1,1 - 0,3%	9,10,11
<b>Prognosis</b>			
healed	< 9 month	50%	1
	< 2 years	80%	} 1,2,10
	< 5 years	92%	
<b>Recurrence</b>			
	< 1 year	30 - 57%	2

P.S. Change the following in above Table I. Prevalence 1.5 - 3%; 1.1 -0.3%.

The prevalence of venous ulcers varies between 1.5 and 3% in the population<sup>1</sup>, and in 4-5% of individuals older than 80 years<sup>2,7</sup>. This was in keeping with the findings that 1-2% of the adult population either has or had a venous ulcer<sup>5,8</sup>. In the Western countries, a prevalence of active venous ulcers in the general population older than 18 years was reliably estimated to be 0-1-0.3%<sup>9,10,11</sup>. An ulcer is encountered 2 to 3 times as often in women of all age groups<sup>12,13</sup>. There is a clear increase with age. Chronic ulcers below the age of 60 years are unusual<sup>1</sup>. Since venous leg ulcers in young patients are nearly always associated with severe CVI as congenital malformations/ absence of the vena cava and/or non- recanalised deep venous thrombosis, they

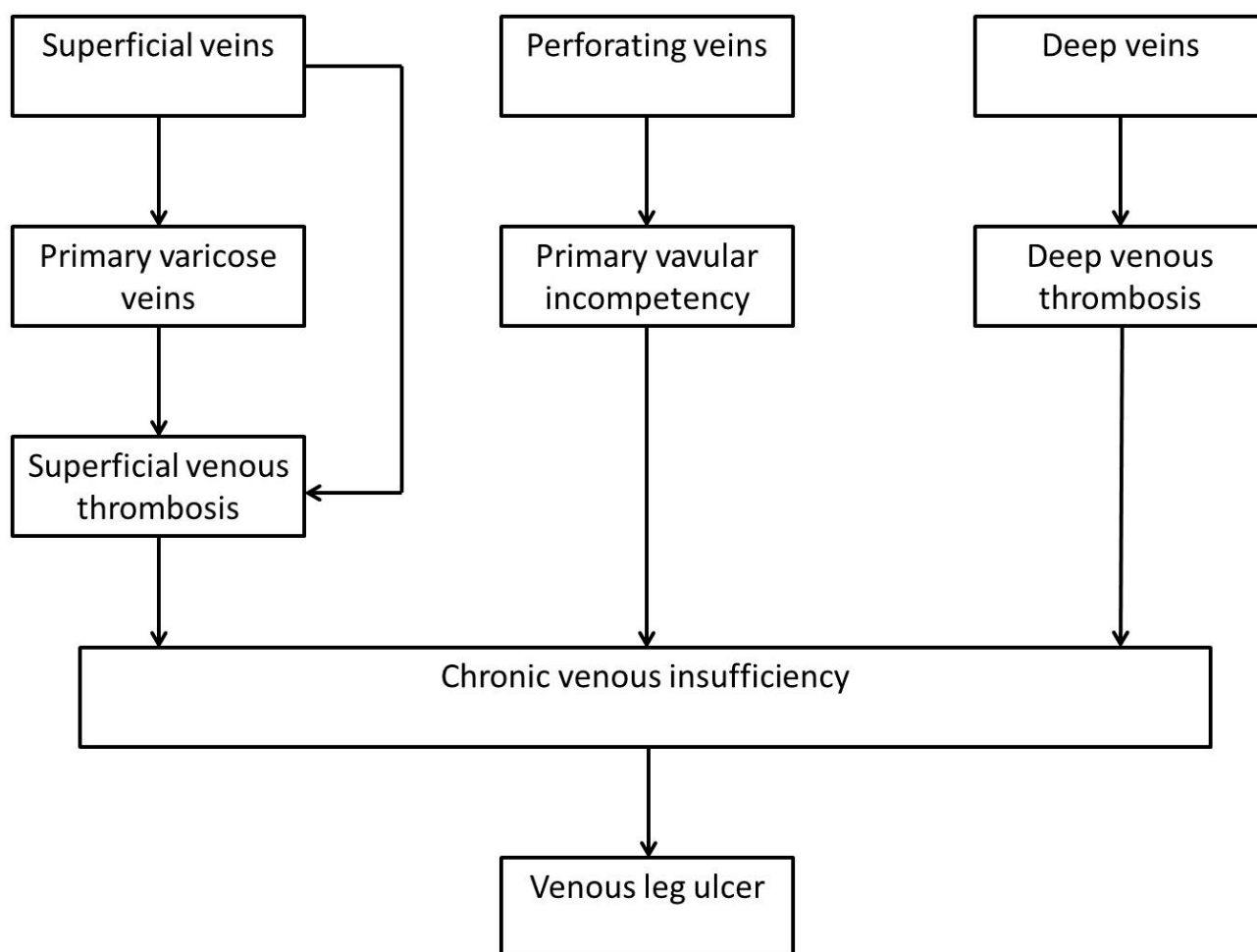
should not be included in clinical therapeutical studies. Leg ulcers in white atrophy in Klinefelter patients also occur due to plasminogen inhibitor 1 deficiently<sup>14</sup>. The prevalence among the elderly may be quite high (12.6% of leg ulcers (C5-C6) in a Swedish rural population older than 70 years<sup>15</sup>. However, up to 50% of leg ulcers are caused by superficial venous insufficiency<sup>16,17,18</sup>. Early treatment of varicose veins with significant reflux<sup>19</sup> may thus prevent 50% of all venous leg ulcers. Co-morbidity plays an important role at least in the developed world and there is a very high correlation between obesity and venous leg ulcers<sup>20,21</sup>.

The prevalence of active and healed ulcers together is about 0.6-1%<sup>1,5,22</sup>. The prognosis is not very good. The incidence of ilio caval venous obstruction is possibly a significant contributor for venous hypertension in advanced disease<sup>23</sup>. About 50% of the treated ulcers had healed within 4 months<sup>1</sup>, about 20% had still not healed after 2 years and about 8% had not healed after 5 years<sup>1,2,10</sup>. The annual recurrence was 6-15%<sup>10</sup>. The total risk of recurrence was about 3-15%<sup>1</sup> and the risk of recurrence within the first year was 30-57%<sup>2</sup>. The majority of the ulcers recurred at least once. Carpentier et al reported no significant difference between the prevalence of varicose veins in different areas in France. No data was available on leg ulcers<sup>24</sup>, but a consistent difference between sexes was noted; 50.5% of those affected were women and 30.1% were men. Key data are shown in Table I

## **1.2 Etiology**

Venous insufficiency was noted to be the most important cause in a large number of venous ulcers. In addition, arterial insufficiency and arteriosclerosis, diabetes mellitus, vasculitis, malignancy, infections and other less frequent causes for ulceration may accompany venous disease in up to almost 20% of the cases<sup>25</sup>. In a large number of cases, long-term complications of deep venous thrombosis, the so-called post-thrombotic syndrome, may lead to venous ulcers.<sup>25</sup> The post-thrombotic syndrome is a special part of CVI in which the underlining etiological event is a venous thrombosis<sup>26</sup>. Estimates vary (as do the used definitions), but on the average, 1 in 3 patients who suffers from a deep venous thrombosis develops post-thrombotic complications in the subsequent 5 years. The chance of developing CVI after a thrombotic leg, thus a post-thrombotic syndrome, is about 50% lower when medical elastic compression hosiery (MECH) is worn<sup>27,28,29</sup>. There are different mechanisms for pumping the blood effectively against the pull of gravity. The cooperation between the venous valves and the calf muscle pump is the most important factor.<sup>26</sup> The blood is pumped towards the heart while walking when the valves prevent the backflow. As a consequence, the venous pressure drops when the person is walking. A reflux of the blood occurs when this mechanism fails (in upright position) and an increased pressure develops in the veins of the lower legs (increased ambulatory venous pressure or venous hypertension). All the structures of the venous system may play a role in CVI and thus the venous leg ulcer (Fig. I).





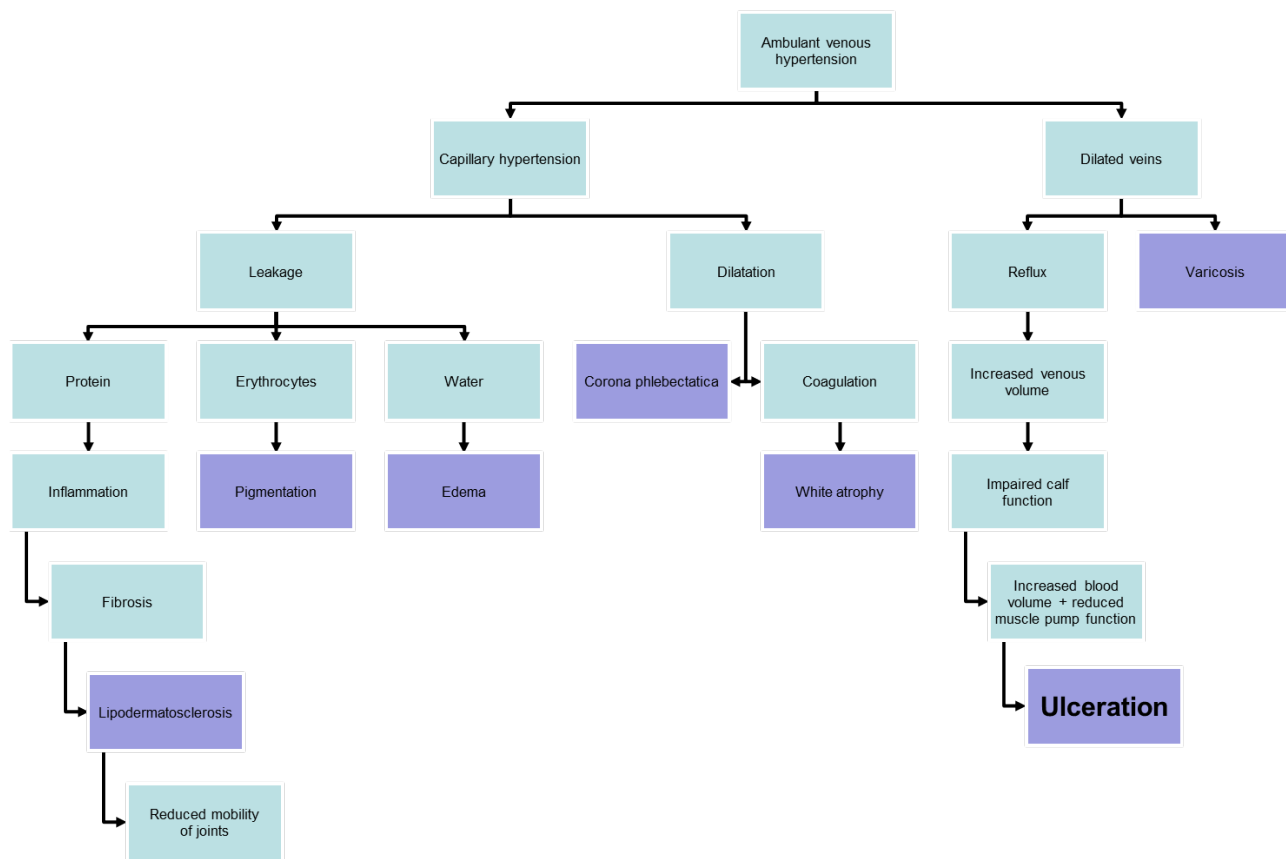
**Figure 1: Pathways from vein to ulcer**

Varices will develop initially because of the alterations in the vein wall. Incompetence will develop both in the descending and the ascending processes<sup>30</sup>.

Several of the previously mentioned studies reported that varicose veins were more common in women than in men. This difference may be explained by selection bias, since women consider varicose veins as a cosmetic problem more often than men and consult a physician more often and therefore are more likely to participate in studies. Most general population studies failed to demonstrate a sex difference. However, more advanced chronic venous disease (CVD) occurs equally in both sexes. It may lead to leg ulceration as the end stage (Fig. 1). Venous leg ulceration has a lifetime prevalence of 1% and a prevalence of active ulceration of 0.3% in the adult Western population. The prevalence of venous leg ulceration increases with age. Chronic ulceration in those younger than 60 years is unusual and often related to severe deep venous insufficiency. The venous pressure will also increase in the venules and in the capillaries upon further decompensation. As a result of this increased intra-capillary pressure, the capillary filtration fraction will increase and edema will develop because of the leakage of fluid. Besides the leakage of fluid, there is also a leakage of high molecular weight substances such as fibrin. This can be observed as a "cuff" around the capillaries. Initially, it was thought that these fibrin cuffs formed a barrier for the diffusion of oxygen resulting in local anoxia and ulceration<sup>31</sup>. However, this thought was discarded by the fact that fibrin cuffs around capillaries were demonstrated in other skin diseases without any disturbance in the transcutaneous oxygen tension<sup>32</sup>. The trapping of leukocytes in the capillaries and the release of free radicals were also proposed as a possible explanation<sup>33,34</sup>.

Furthermore, the transmission of high venous pressures to the dermal microcirculation results in the stimulation of an inflammatory process in which cytokine and growth factor release leads to leukocyte migration into the interstitium and the triggering of further inflammatory events<sup>34,35</sup>. This process is associated with the intense dermal fibrosis and tissue remodelling seen in CVI<sup>36</sup>.

Thrombus formation in the capillaries of the skin was not only observed in white atrophy lesions, but also in other cutaneous manifestations of CVI at microscopy. This was also proposed as an explanation for the ulceration. Finally, it was demonstrated that the fibrin cuffs around the venous leg ulcer do not capture oxygen, but probably growth factors<sup>37</sup> so that these are less active in the wound. All these contributory factors in the development of a venous leg ulcer are combined in the Rotterdam model<sup>19,26</sup>



**Fig. II: The Rotterdam model explains the pathways from venous hypertension to venous leg ulcer (clinical symptoms are in dark blue).**

Some authors speculated that a biofilm may play an important role<sup>38</sup>.

All the structures of the venous system may contribute in CVI and thus the venous leg ulcer (Fig. I).

Obesity is certainly a risk factor for venous leg ulcers. Obesity may cause venous hypertension and later venous ulcers, even without valve incompetence or permanent obstruction of the venous system<sup>21</sup>. Dependency is another negative co-factor. The muscle pumps will not function due to immobility and consequently venous hypertension will occur. In both cases the venous valves can

be patent. This is also one of the important reasons to combine the classical physical examination with the technical investigations, especially Duplex ultrasound techniques. The Duplex examination is for this reasons best performed by the physician and a technician.

### **1.3 Symptomatology**

The venous leg ulcer arises either "spontaneously" or often after a minor trauma. The complaints of the patient as a result of the ulcer may vary from less pronounced to very pronounced. Although many textbooks mention the opposite, venous leg ulcers can be painful. The complaints of pain are particularly prominent in the ulcerative phase of white atrophy or if accompanied by other factors such as an infection.

Clinically, venous leg ulcer is a part of CVI. Patients with CVI develop various skin abnormalities like pigmentation, corona phlebectatica, white atrophy and dermato-et liposclerosis (Fig. II) over a period of time. The percentage of patients who develops symptoms remains unknown because it has never been properly mapped (investigated?).

The venous ulcer is generally located on the medial and less frequently on the lateral side of the ankle. A particular form is the ulceration in acroangiodermatitis<sup>2,39</sup> of the forefoot in patients with a foot pump incompetence. If the ulcer is located on another part of the lower leg, then one must strongly suspect that causes other than venous insufficiency play a role. The clinical characteristics of CVI are generally known. For the sake of completeness they are mentioned here once again: varicosity, edema, corona phlebectatica, hyper-pigmentation, dermato- et liposclerosis, white atrophy, secondary lymphedema stasis dermatitis, which can be classified better as eczema cruris due to CVI and the ulcer<sup>40</sup>. The changes in the skin in venous insufficiency are a result of changes in the macro- and microcirculation (Fig. II). It is unclear why an extensive dermato- et liposclerosis is formed in one patient, whereas a white atrophy is prominent in another patient. Local factors possibly play a role in this and should be investigated further.

### **1.4 Quality of life**

Venous ulcers have a substantial impact on patients' lives and affect most issues of health-related quality of life (HRQOL) such as bodily pain, health transition, mental health, social functioning and vitality<sup>41,42,43</sup>. Treatment and especially healing of venous ulcers results in a significant improvement in these areas. Nonetheless, a few specific HRQOL instruments have been developed. Studies indicated that these instruments were suboptimal and that generic instruments such as the SF-36, SF-12 and EuroQoL-5D were recommended for the purpose of measuring the impact on patients' lives, for time being<sup>44,45</sup>. Today the society requires treatment evaluation, which includes patient- related outcome parameters.

## **Literature**

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## Chapter 2 – Diagnostics

### 2.0 Introduction

5 The differential diagnosis of the venous leg ulcer is large. However, there are several diagnoses that are considered to occur most frequently. It is essential to immediately establish an adequately correct diagnosis as soon as possible considering that different diagnoses have totally different approaches and treatments. An incorrect diagnosis may have dramatic consequences for the patient in several situations.<sup>1</sup>

### 10 2.1 Anamnesis

#### Scientific basis

A good anamnesis is indispensable. Many patients with a leg ulcer have an extensive previous medical history and often also comorbidity. Good studies on the value of specific items for the anamnesis are lacking.

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#### Conclusion

Level 4	Good studies on the value of specific items for anamnesis are not available. Nevertheless, a good anamnesis is indispensable. Level D
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#### Other considerations

20 Field experience and consensus within the various disciplines indicated that the previous medical history as well as the family anamnesis and the specific aspects of the ulcer must be dealt with extensively in the anamnesis<sup>2</sup> (see Table I).

**Table II: Subjects for leg ulcer anamneses**

<i>Subject</i>	<i>Special attention</i>
<i>Previous medical history</i>	<i>Varicosity and treatment of varices</i>
	<i>Venous thrombosis (superficial and deep)</i>
	<i>Leg ulcer</i>
	<i>Peripheral arterial vascular disorder (including complaints of intermittent claudication)</i>
	<i>Diabetes mellitus</i>
	<i>Rheumatoid arthritis</i>
	<i>Extensive leg trauma</i>
	<i>Medication use</i>
	<i>Life style: nutritional status, alcohol, mobility (walking, sports, etc.)</i>
<i>Family anamnesis</i>	<i>Varicosity</i>
	<i>Venous thrombosis</i>
	<i>Leg ulcers</i>
	<i>Vascular disorder</i>
<i>Specific aspects</i>	<i>Duration of the ulcer</i>
	<i>Pain</i>
	<i>Previous treatment</i>

	<i>Fever and other symptoms of infection</i>
	<i>Agility of the ankle joint</i>

### Recommendation 1

Anamnesis is not neglected and the items in Table I are diseases (see Table I).

## 5 2.2 Physical examination

Physical examination is regarded as extremely important. Since 1994, a new classification for chronic venous diseases was prepared by an international working group called CEAP. This classification replaced the up to then widely used Widmer classification.<sup>3</sup> Although this classification is easier and in special conditions also today helpful like in PTS<sup>4</sup> the international experts today recommend using the CEAP classification. In the CEAP classification, the “C” stands for Clinic, the “E” for Etiology, “A” for Anatomy and the “P” for Pathophysiology (Table II).

Although many physicians only use the “C” of the CEAP, it is recommended to use the full CEAP for a correct diagnosis of all venous diseases including the venous leg ulcer<sup>5</sup>.

since CVI is characterized by venous hypertension, ambulatory venous pressure measurements in is principal the gold standard.<sup>6</sup> However, it was proven that the “C” in CEAP correlates well with the ambulatory venous pressure measurements<sup>7</sup>. As the varicose of the saphenous vein is normally not visible at clinical examination and the “C” has been determined only by visual examination and not by additional Duplex investigation, this incompetence may be missed. So the clinical interpretation alone may be misleading<sup>5</sup>. The international CEAP classification was designed to obtain an unequivocal description of the abnormalities in patients<sup>8</sup>. This classification was revised in 2004<sup>9</sup>. The physical and technical examination is the leading feature in this classification.

**Table III: CEAP classification for chronic venous diseases**

C	E	A	P
Clinical status (clinic)	Etiology	Anatomy	Pathophysiology
C0 no visible abnormalities			
C1 teleangiectasias or reticular veins	E <sub>p</sub> primary	A <sub>s</sub> superficial	P <sub>r</sub> reflux
C2 varices	E <sub>s</sub> secondary	A <sub>p</sub> perforating	P <sub>o</sub> obstruction
C3 edema,	E <sub>c</sub> congenital	A <sub>d</sub> deep	P <sub>r,o</sub> reflux and obstruction
C4 Changes in skin and subcutaneous tissue secondary to CVD a Pigmentation or eczema. b Lipodermatosclerosis or atrophie blanche.	E <sub>n</sub> no venous cause identified	A <sub>n</sub> no venous location identified	P <sub>n</sub> no venous pathophysiology identified
C5 healed ulcer			
C6 active, open ulcer			
S symptomatic, including			

ache, pain, tightness, skin irritation, heaviness, muscle cramps and other complaints attributable to venous dysfunction			
A asymptomatic			

As arterial incompetence is quite often present besides CVI in all patients, an ankle/arm index are two pressure measurements that must be performed.

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### **Recommendation 2**

The working group recommends the use of the full CEAP classification in all cases. This is done via a combination of physical examination and technical aid (especially Duplex). In addition, the size, the site and the characteristics of the ulcer should be recorded. An ankle/arm index must be determined.

## **2.3 Supplementary investigation**

### **2.3.1 Venous investigation**

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#### **Venous Doppler**

##### **Scientific basis**

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Doppler sonography is a simple, practical and cheap screening technique for the detection of blood flow direction.

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Comparative studies have mainly been done with descending phlebography, duplex diagnostics and venous pressure measurements. The sensitivity and the specificity of Doppler diagnostics in uncomplicated varicosis of the greater saphenous vein (GSV) and the saphenofemoral insufficiency are high (>92%). However, the sensitivity and especially the specificity are clearly lower in case of the recurrence varicosis of the GSV, or in reflux in the fossa poplitea and in venae perforantes (<70%)<sup>10,11,12,13,14</sup>. Besides, Doppler diagnostic highly depends on the investigator. The value of the Doppler diagnostic is doubtful considering that in a considerable number of cases of venous leg ulcers there is an insufficiency in the flow detection in fossa poplitea, in the deep venous system or an insufficiency in the venae perforantes. Doppler is indispensable to exclude arterial occlusion by measuring the ankle-brachial-pressure index (ABPI).

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##### **Conclusion**

Level 2	Doppler has a low sensitivity and a low specificity in the diagnostics of the deep venous system and the venae perforantes.  B Raju 1990 <sup>10</sup> ; McMullin 1992 <sup>12</sup> ; Rautio 2002 <sup>13</sup> ; Negus 2005 <sup>14</sup>
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### **Recommendation 3**

The use of Doppler in the diagnostics of venous leg ulcer is not advised for routine investigation of the deep venous system and the venae perforantes.

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#### Recommendation 4

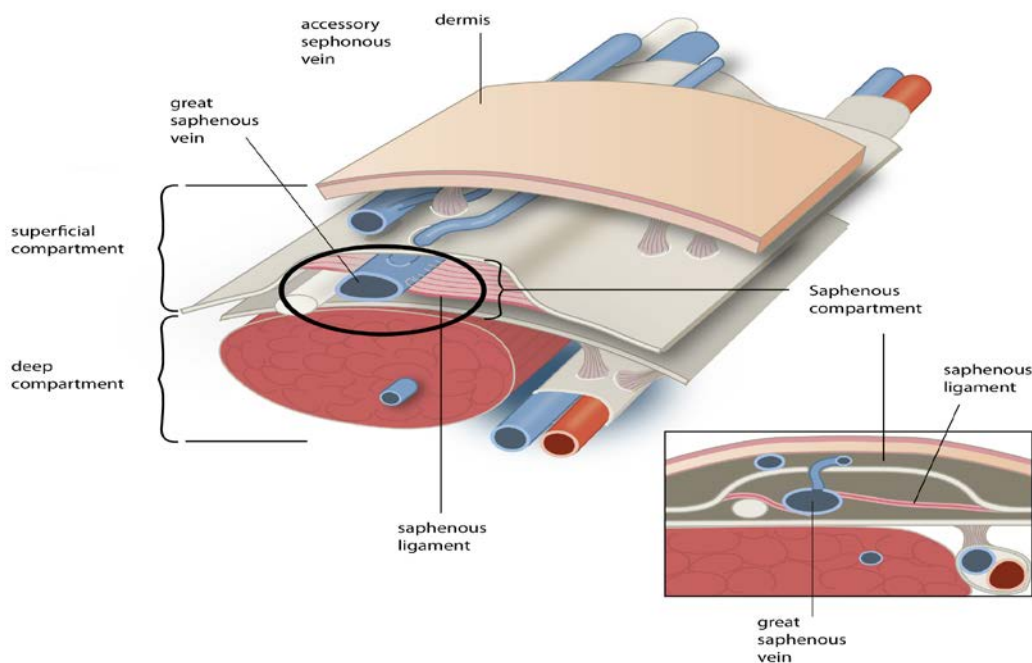
ABPI should always be determined before pressure therapy is given

#### Venous Duplex

##### 5 **Scientific basis**

Duplex ultrasonography is a combination of B-mode echography and Doppler sonography. The technique was initially utilized in the diagnosis of deep venous thrombosis. It was Van Bemmelen who, towards the end of 1980s, demonstrated that the diagnosis of varices and venous insufficiency could be conducted reliably with duplex<sup>15</sup>. One could look at the diameter, the duration of the reflux, the presence of flow and the compressibility of the vein. The nerves and the lymph nodes can also be visualized. Duplex has led to a more precise anatomical definition. It was proven that the presence of older studies is rare because a good definition is lacking. In this Duplex definition of the greater saphenous vein, it is obligatory present in the so-called saphenous compartment. (Fig. III).

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**Fig. III: An illustration of the saphenous department (with permission)**

20 Duplex investigation should be performed on a strictly standardized basis in the standing position<sup>16</sup>. For investigation of the deep system up to the v. cava the patient is put in supine position<sup>17</sup>. The duration of the reflux in normal proximal veins of the leg is <1 sec. and <0.5 sec. in the distal veins. There is no clear demonstrable difference between the induction of the reflux signal (in the proximal deep veins) between the classic Valsalva maneuver and the "rapid" cuff inflation<sup>18</sup>. The former is preferred considering its simplicity.

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Similarly to Doppler, the diagnostic strongly depends on the investigator. The variation coefficient of the reflux measurements is considerable (30-45%), but the inter-observer reliability is good

(kappa 0.86) if the above-mentioned cut-off points of the reflux are strictly adhered to. Adopting a uniform cut point of 0.5 second for pathologic reflux can significantly improve the reliability of reflux detection. Implementation of a standard protocol should elevate the minimal standard for agreement between repeated tests from the current 70% to at least 80% and with more rigid standardization, to 90%<sup>19</sup>. It is also important to note that with duplex investigation is possible to find crossover reflux routes in 25 of the 54 (46%) legs with lateral and in 11 of the 103 (11%) legs with medial ulceration<sup>19</sup>. Although it is difficult to correlate Duplex to another technique, comparative studies on clinical investigation, venous pressure measurements, plethysmographic techniques and descending phlebography were conducted. The best correlation was found using descending phlebography, which demonstrated a sensitivity of 79-100% in investigations on reflux in the deep system. The specificity was clearly lower (63-88%)<sup>20</sup>.

Duplex scanning for the detection of deep venous insufficiency correlated well with descending phlebography. The sensitivity (79-100%) was good, but the specificity (63-94%) was somewhat lower<sup>18</sup>. The full CEAP classification can be established only if Duplex has been performed. Extensive knowledge of the venous anatomy is mandatory to perform venous Duplex investigation. For Duplex investigation in Phlebology a guideline is available both for the superficial<sup>9</sup> and the deep system<sup>17</sup>.

## Conclusion

Level 2	It was demonstrated that duplex diagnostic had high sensitivity and specificity in the diagnostics of the superficial and deep venous system of the legs. A2 Baker 1993 <sup>21</sup> B Lurie F 2012 <sup>22</sup> C Magnusson 1995 <sup>11</sup>
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## Other considerations

A disadvantage of the duplex diagnostics is that there are patients in whom the technique may be laborious to perform because of mobility problems. Obesity complicates the investigation. However, the investigation is less burdensome for the patient, relatively cheap and may be repeated easily. Furthermore, duplex diagnostic is the standard venous investigation and is the gold standard today, which allows a further classification of chronic venous insufficiency and classification-related treatment. Duplex has also become important in ultrasound guided endovascular therapies.

## Recommendation 5

Duplex investigation performed in the standing position is the preferred technique to unravel the hemodynamic disturbances in patients with a venous leg ulcer.

## Phlebography

### Scientific basis

Phlebography is a radiological technique in which contrast fluid is injected into the venous vascular system. A distinction between ascending phlebography, descending central phlebography and varicography is made. In the ascending phlebography, contrast fluid is injected into a vein in the back of the foot, whereas in the descending phlebography, the contrast fluid is injected into the

femoral vein, after which a Valsalva maneuver is performed. Descending phlebography was compared with deep venous pressure measurements. The sensitivity was good (70-100%), but the specificity was relatively low (40-75%)<sup>11</sup>.

Duplex diagnostic has largely replaced phlebography. However, phlebography may still be valuable in distinguishing between primary and secondary varices, in identifying the level of obstruction in the femoral and the iliac veins, in detecting incompetence of the gastrocnemius veins, v. ovarica and in determining the level of reflux in the deep venous system as well as the status of the valves<sup>23</sup>. It is also possible to combine phlebography with MRI in newer systems and make it three-dimensional.

## Conclusion

Level 2	Descending phlebography has a high sensitivity but a low specificity for specifying venous incompetence. B Raju 1990 <sup>10</sup> , Mantoni 2002 <sup>23</sup>
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## Other considerations

The investigation is burdensome for the patient and is expensive.

## Recommendation 6

Descending phlebography is not the diagnostic tool of first choice for a leg ulcer. The technique should be used only on special indication. The sensitivity is high.
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## *Direct venous pressure measurement*

### Scientific basis

An increased ambulatory venous pressure causes venous pathology. There is a clear correlation between this pressure and the extent of pathology<sup>24,7</sup>. This pressure can be invasively measured directly by means of a cannula in a superficial foot vein. This technique has been standardized recently<sup>7</sup>. There is a good correlation between this pressure in a foot vein and the pressure in the deep veins at the ankle height<sup>25</sup>. Superficial venous insufficiency can be distinguished from deep venous insufficiency by occluding the superficial system by means of a tourniquet<sup>26</sup>. There is a good correlation between the C in the CEAP classification and the venous pressure<sup>7</sup>. The direct venous pressure measurement is seldom used because of its invasive character and the fact that the procedure is complicated and correlates well with the CEAP.

### Recommendation 7

Direct venous pressure measurement is not recommended for routine use in CVI and in patients with venous leg ulcer.
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## Indirect venous pressure measurement

### Scientific basis

Plethysmography is a method in which volume changes are measured. Under certain conditions these changes can be translated to pressure. However, one has to realize that the pressure/volume relation is far from linear. This technique includes strain gauge<sup>27</sup>, light<sup>28</sup>, air<sup>29</sup> and

water<sup>30</sup> as substrate for the measurements. All techniques are complicated and temperature dependent<sup>27,28,30,31,32,33</sup>.

### Photoplethysmography

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#### **Conclusion**

Level 3	Plethysmography investigation can provide information on deep venous insufficiency and on the function of the calf muscle pump. An increase in the venous refill time measured after occlusion of the superficial system may indicate a negative influence of the superficial varicosis on the ambulatory venous pressure.  Ref C Wienert 1982 <sup>28</sup> ; Blazek 1989 <sup>31</sup> ; Nicolaidis 1987 <sup>32</sup> ; Shepherd 2011 <sup>33</sup>
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#### 10 **Recommendation 8**

As the “C” in CEAP correlates well with the venous pressure, venous pressure measurements are hardly necessary.

#### **Recommendation 9**

Photoplethysmography is not advised for routine investigation because of its low sensitivity and specificity. The remaining plethysmography methods have no additional value in daily practice.

#### 15 **2.3.2 Other investigation**

Systolic ankle pressure index measured by hand held Doppler

##### **Scientific basis**

20 It was reported in a number of studies that up to 30% of the total number of patients with a leg ulcer suffer from peripheral arterial vascular incompetence. The ulcers hereby may be the result of this peripheral arterial vascular disorder alone or in combination with venous insufficiency. Location of the ulcer may be an indication for peripheral arterial vascular disorder. Therefore, the chances of this occurring in combination with ulceration of the foot are considerably higher than when ulceration is around the ankle<sup>34</sup>. This is only 1 reference! More references required. Please check!!!

25 A supplementary investigation of the arterial influx is required for the correct estimation of the presence and the seriousness of this peripheral arterial vascular disorder as the anamnesis and the physical examination are not sufficient. The palpation of the ankle artery at the back of the foot appeared to be insensitive, even when carried out by experienced hands, and does not exclude arterial disorder<sup>35,36,37</sup>. Measuring the systolic ankle pressure in comparison with the systolic arm pressure and calculating the systolic ankle pressure index using a Doppler instrument provides a reliable indicator for the presence of an arterial obstruction. The Ankle brachial systolic pressure Index (ABSPI), the so- called ankle/arm index is calculated: systolic ankle pressure divided by the

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systolic brachial pressure. A prerequisite for a valid assessment is that the measurements should be performed in a standardized manner<sup>37</sup>. An arterial abnormality in an arteriogram is largely excluded (chance >95%) if the systolic ankle pressure index is > 0.8. Measuring the systolic ankle pressure index is not always reliable in patients with diabetes mellitus because compression of the arteries may not be possible due to medial sclerosis.

**Conclusion**

Level 3	An estimated 25% of the patients with a leg ulcer have arterial insufficiency <sup>38</sup> . The palpation of the ankle artery at the back of the foot is an unreliable test. A systolic ankle pressure index does provide a reliable indication.
	C    Stoffers 1996 <sup>37</sup> Forssgren A 2012 <sup>36</sup>

**Recommendation 10**

It is recommended that patients with a leg ulcer should be subjected to an additional investigation for ruling out concomitant arterial occlusive disease by measuring systolic ankle-brachial-pressure index (ABPI). Further arterial investigation may be undertaken on indication.

**Microbial cultures and antibiotics**

**Scientific basis**

Most of the leg ulcers are either contaminated or colonized by bacteria or yeast over a period of time. In larger studies, positive results of cultures were reported in all ulcers<sup>39</sup>. More refs? Please check!! However, others found negative results in 10-15%.<sup>40</sup> There was a clear relationship between the size of the ulcer, the duration of the ulcer and the age of the patient<sup>41</sup>. Staphylococcus aureus, Streptococci (not group A beta hemolytic) and Pseudomonas aeruginosa were observed in most cultures. The presence of anaerobic bacteria was reported in up to 30% of the cases in one study<sup>42</sup>. Finally, Candida albicans and other fungi were also encountered in 15 to 30% of the ulcers<sup>43</sup>.

It was reported in a number of studies that there was no relationship between a positive bacterial culture result and a slow wound healing<sup>44,45,46,47,48</sup>. Various authors then also concluded that there was no reason for routine cultures in a venous leg ulcer. However, a culture is done before surgery and in the interest of the policy for detecting MRSA. A sample for culture is always obtained if there are signs of cellulitis or erysipelas, increased pain, an increase in the size of the ulcer, erythema around the wound and a purulent exudate. There is one Cochrane review in which the effect of antibiotics in the treatment of ulcers was investigated. Based on five different trials there was no evidence to support the routine use of systemic antibiotics to promote healing in venous leg ulcer. However, there was no statistically significant difference between the patients who were treated with antibiotics and those who were not.

**Conclusion**

Level 3	Standard sampling for bacterial colonization has no therapeutic consequence and thus meaningless. Culturing and eventual prescription of antibiotics is only indicated if there are signs of an infection in the wound.
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B Alinovi 1986<sup>40</sup> Moore 2010<sup>47</sup>

### Recommendation 11

A swab from a venous leg ulcer for culture is warranted only if there are signs of an infection, before surgery on leg ulcers and for MSRA detection. Oral or intravenous treatment with antibiotics should then also be considered.

## 5 Biopsy

### Scientific basis

If an ulcer has an atypical appearance or responds inadequately to the therapy, then the possibility of another diagnosis such as a malignancy vasculitis, other dermatological diseases or arteriosclerosis (Martorell ulcer)<sup>49</sup> should be considered and a skin biopsy should be obtained<sup>50,38</sup>. In one trial, chronic leg ulcers referred to tertiary care center contained 10.4% malignancies. This data certainly does not reflect the normal venous leg ulcer patient group.

### Conclusion

Level 3 A biopsy (V-shaped) from the edge of the wound may rule out the possibility of a malignancy, vasculitis or arterial sclerosis if the venous leg ulcer responds inadequately to therapy or has an atypical appearance.

C Yang 1996<sup>50</sup> Vuerstaeck 2010<sup>49</sup> Senet 2012<sup>38</sup>

### Recommendation 12

Taking multiple biopsies should be considered if an ulcer does not respond or responds inadequately to therapy and has an atypical appearance.

## 20 Contact allergy investigations

### Scientific basis

Eczema cruris in CVI occurs frequently and is often unjustly diagnosed as erysipelas. A possible contact allergy must always be considered in the case of patients with a long previous history of recurring ulcers. It was shown in various studies that in the case of contact allergies there was generally an allergy to components such as Peru balsam and lanoline in wound ointments, topical antibiotics, wound dressings and bandages whereby there was a clear relationship between the duration of the ulcers and the occurrence of contact allergies<sup>51,52,53,54,55,56,57,58,59</sup>

One should always consider the possibility of contact allergy when there are indications of slow wound healing. This often manifests in the form of eczema.

Eczema in CVI and leg ulcer patients is not only caused by contact allergy. There is evidence that venous hypertension itself causes eczema. Eczema cruris due to CVI (stasis dermatitis) has been reported<sup>60</sup>.

## Conclusions

Level 3	A contact allergy is often present in patients with persistent or recurrent ulcers. Eczema or a slow healing of the wound may indicate this.  C Wilson 1991 <sup>52</sup> ; Katsarou-Katsari 1998 <sup>53</sup> ; Lange 1996 <sup>55</sup> ; Tosti 1996 <sup>56</sup> ; Schliz 1996 <sup>57</sup> , Zmudzinka 2006 <sup>58</sup> ; Barbaud 2009 <sup>59</sup>
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## Recommendation 13

The recommendation is to carry out a test with a series of allergens that are present in products for treating wounds and wound dressings in addition to the European standard series in all cases of leg eczema in CVI when contact allergy is suspected.

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## Chapter 3 – Compression therapy

### Introduction

Compression therapy is still the cornerstone in phlebological treatment. Compression therapy may be carried out in different ways. On one hand, with bandages with more or less elasticity (without stretch, short stretch or long stretch) and on the other hand, with medical elastic compression hosiery (MECH). Finally, the compression may also be pneumatic and provided by a pneumatic pump, but this is not further commented on in this guideline.

Some still make a distinction for the medium stretch bandages, but these are not encountered in medical literature. In particular, bandages may also have an adhesive layer, in which case the bandage can only be used once because such an adhesive has a large influence on the elasticity of the bandage. Generally, the bandages do not stretch in the breadth, but this is not mentioned in the encountered literature. Several layers of bandages may be placed over each other to increase the compression by increasing the hysteresis of the bandage. Generally, bandages of the same quality are involved. A system, popular in England, uses a combination of short stretch and long stretch compression known as four-layer-bandage; of course the short stretch part of this bandage determines the stretch quality.

Medical elastic compression hosieries (MECHs) that are medically approved always have a decreasing compression gradient from distal to proximal. They are divided into compression classes, whereby the division is determined by the compression of the MECHs on the skin above the malleoli (so called interface pressure). The Comité Européen de Normalisation (CEN) (ENV 12718) has set a standard for MECHs in Europe. The compression classes are (based on the B-size): pressure class A (light) 10-14 mm Hg (13-19 hPa), class I (mild) 15-21 mm Hg (20-28 hPa), class II (moderate) 23-32 mm Hg (31-43 hPa), class III (strong) 34-46 mm Hg (45-61 hPa), class IV (extra strong) >49 mm Hg (>65 hPa)<sup>1</sup>. One should realize that an anti-thrombosis stocking is of class I without pressure gradient. These stockings are meant for bed-ridden individuals and remain beyond the scope of this discussion. Various options for compression are compared in this chapter.

### 3.1 Compression versus no compression

#### Scientific basis

A randomized controlled trial comparing treatment outcome of two compression bandaging systems and standard care without compression in patients with venous leg ulcers was conducted by Wong et al <sup>1a</sup>. The results showed that compression was feasible in elderly community care patients in Hong Kong and is currently implemented as part of standard venous leg ulcer treatment.

The garment gives a certain pressure to the leg. Normally this pressure is expressed as interface pressure: the pressure which is exerted from the garment on the skin. The tension/pressure/circumference relation<sup>2</sup> is essential to understand the high pressure differences on various locations at the lower leg and formulated in Laplace law:

$$P = \frac{T}{R}$$

P: interface pressure in mmHg or hPa

TW: tension (n) per distance unit  
 R: radius in m  
 α: a coefficient (proportional)

- 5 The Laplace law is only useful in static condition because during walking the circumference of the calf changes constantly and a dynamic formula for this lacking. In the treatment of venous diseases, compression therapy is ambulatory compression with the combination of walking by which the muscle pumps are active and the pressure exerted by compression (elasticity) of the device. Ambulatory compression is more effective as static compression.
- 10 During walking the calf circumference changes<sup>3</sup> leading to more pressure when the circumference increases and less interface when it decreases. As all materials are under the influence of hysteresis, the garment will vary in its stiffness. This hysteresis is a kind of inborn resistance. Due to this hysteresis, the extension of the garment during walking cannot directly follow completely leading to a relative increase in the interface pressure. The circumference changes during walking are approx<sup>1</sup> H2 for humans. So the stiffness and the hysteresis combined will result during ambulatory compression in that the interface pressure will increase disproportionately. This is mainly depends on the stiffness of the garment. This character of compression is known as the dynamic stiffness index<sup>3</sup>. Higher this index is more effective is the compression.
- 20 Compression systems for leg ulcers have been compared in various systematic reviews. It appeared that the same publications were constantly included in some reviews. The conclusion endorsed by many is that healing is faster with the use of compression than without<sup>4,5,6,7,8,9,10,11,12,13,14</sup>. There are no studies in which the reverse was reported. Compression therapy is also consistently recommended in international guidelines<sup>5,7,8,9,10,11,12</sup>. There are reviews from which one can deduce that there is indirect evidence that compression leads to faster healing, although few good studies are available in which compression was compared with no compression<sup>15,16,17</sup>.

**Conclusion**

Level 1	Compression therapy is an effective treatment in uncomplicated venous ulcers. A1 Fletcher 1997 <sup>4</sup> ; Cullum 2001 <sup>5</sup> ; SIGN 1998 <sup>7</sup> ; O'Meara 2012 <sup>17</sup>
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**Recommendation 14**

Compression therapy is the treatment of first choice in an uncomplicated venous leg ulcer.

**3.2 Comparison of different types of compression bandages**

**Scientific basis**

A lot of studies in which various types of bandages were used are compared in different reviews. A generally accepted conclusion is that a high compression is more effective than a low compression in the healing of a venous leg ulcer<sup>4,6,9,11,12</sup>. Venous reflux can be reduced more effectively with a short stretch bandage than with an elastic one<sup>18</sup>. A short stretch compression and Unna's boot supports the pump function of the calf muscles better than a long stretch compression<sup>19,20</sup>.

Generally, more layers of a bandage are applied on top of each other because a single layer bandage provides less effect with the same interface pressure than a multiple layer bandage<sup>2</sup>. The hysteresis increase with every layer.

In comparative studies on different types of bandages, multiple layers of different elastic bandages were described to be more effective than a short stretch bandage<sup>5</sup>. More refs. Please check!! A comparison of short stretch bandages with a four-layer-bandage (combination of four different layers of which one is inelastic, thus a high stiffness) showed that after 16 weeks there was healing in 62% of those treated with a four-layer bandage and in 73% of those treated with a short stretch bandage (difference not significant)<sup>15</sup>. It made no difference which bandage was used<sup>4,5,6,8,9,10,11,23</sup>, provided it was correctly applied<sup>4,5,6,7,8,10,12</sup>. In recent years special compression stockings for venous leg ulcers form a serious alternative to bandages. There several good studies proving that ulcer stockings were equal or superior to bandages Refs? Please check!!. Non-elastic compression had a high working interface pressure and low resting pressure because the stiffness was very high. Elastic compression, due to the elasticity, has a high working and also high resting pressure<sup>2</sup>. Non-elastic compression, which has only a high working pressure can therefore be used day and night and elastic only during the day because in supine position there is a serious risk to compromising the arterial influx with elastic compression<sup>21</sup>.

The four-layer-bandage is very popular in the United Kingdom because the care for a patient with a venous leg ulcer is almost exclusively provided by nurses. In contrast to other systems, little specific training or experience is required in the application of a four-layer-bandage<sup>7,8,17,22,23</sup>.

## Conclusions

Level 1	There is no evidence that a particular type of bandage is the best. A bandage must be properly applied and that requires training.  A1 Fletcher 1997 <sup>4</sup> ; Culum 2001 <sup>5</sup> ; Kurz 1999 <sup>6</sup> ; SIGN 1998 <sup>7</sup> ; Agus 2001a <sup>8</sup> ; Vin 2003 <sup>23</sup>
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Level 1	High-pressure compression is more effective than low-pressure compression. Multiple layers of a bandage are required to provide adequate compression.  A1 Fletcher 1997 <sup>4</sup> ; Kurz 1999 <sup>6</sup> ; Agus 2001b <sup>8</sup> ; Vin 2003 <sup>23</sup>
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## Other considerations

Simple, but more expensive bandaging techniques are available for those with inadequate bandaging experience. High pressure elastic bandages are strictly contra-indicated in patients with arterial occlusive disease. The pressure depends on the person who is carrying out the compression and on the elasticity. Long stretch bandages provide a more constant high pressure than short stretch bandages leading to a higher risk for people with arterial occlusive disease.

## Recommendation 15

A properly applied high interface pressure amplitude compression bandage should be used in an uncomplicated venous leg ulcer. A four-layer-bandage is worth considering if the bandaging staff is inexperienced in the application of high pressure bandages.

### **Compression with medical elastic compression hosiery (MECH)**

#### **Scientific basis**

5 It was established in systemic reviews that MECH exerting a pressure that exceeded or was equal to 35 mm Hg may also be used in the treatment of venous leg ulcers<sup>6,9</sup>. The compliance was 70% and few side effects were reported<sup>6</sup>.

10 Special MECHs for the treatment of leg ulcers have been available on the market for a number of years. In two randomized controlled trials results that were even better or at least similar to those with classical compression therapy were reported<sup>24,25</sup>. The special MECH ulcer kit consists of 2 MECHs. One with low interface pressure (worn day and night) and one CEN class II MECH (worn only during the day).

#### **Conclusion**

Level 3	MECH exerting a pressure of $\geq 35$ mm Hg (45 hPa) may also be used in the treatment of an uncomplicated venous leg ulcer. Special so-called leg ulcer MECHs are at least as effective as compression therapy.
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B Mayberry 1991<sup>26</sup>; Erikson 1995<sup>27</sup>

B Junger<sup>24</sup>; Junger<sup>25</sup>

#### **Other considerations:**

15 An important aim in the treatment of leg ulcers is the reduction of edema. Compression therapy is normally used for this. Beside bandages intermittent pneumatic compression therapy is very effective for edema reduction in one day.

## Recommendation 16

20 Reduction of edema may be achieved cheaply and generally quickly when short stretch bandages are correctly applied. Well-chosen and correctly measured MECH may be switched to when the size and the level of exudation of the ulcer allow it.

### **Intermittent pneumatic compression**

25 Intermittent pneumatic compression therapy may be a useful adjunct in ulcer healing<sup>28</sup>. Such supplementary compression may be especially useful for patients with restricted walking ability and those with an arterial component in their ulcer<sup>29,30</sup>. This therapy can be given in day care and is also very effective in edema reduction.

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## Chapter 4 – Treatment of Wounds

### Introduction

The cause of the poor healing of venous ulcers is sought in local abnormalities in and around the ulcer, shortage of oxygen, accumulation of granulocytes and T lymphocytes and a disturbed balance of cytokines and growth factors. Treatment of wounds, in an adverse sense, is subordinate to treating the primary disorder, namely, the increased ambulatory venous pressure. In chronic wound treatment the goal is to transform a chronic (more or less inert) wound into an acute wound, which heals along the cascade of wound healing.

One rapidly comes to the conclusion that very little is known about the effect of the treatment during the various stages of the wound healing when one searches on the treatment of wounds in the databanks and in the textbooks. Nonetheless, we are continuously seeing more results of experimental animal studies into the role of oxygen radicals, cytokines, growth factors and matrix-metalloproteases. One of the problems in developing new wound products is that there is no ideal animal model for a chronic wound. Thus, increased animal wound healing results cannot be transferred to the human situation.

The working group did not use the scheme by the Wound care Consultant Society (WCS) for the description of the treatment of wounds.

### Recommendation 17

The working group is of the opinion that the level of cleansing and exudation are the most important parameters for further treatment policy in the case of venous leg ulcers.

## 4.1 Cleansing

### Scientific basis

Little is known in medical literature on the effects of different cleansing methods. Aggressive surgical debridement is recommended in a prospective<sup>1</sup> and a retrospective (prospective? Please check title!) study<sup>10</sup> in chronic venous leg ulcers. The results of the prospective study<sup>1</sup> showed that the presence of dense fibrosis and high levels of mature collagen in deep tissue specimens were significant correlative factors in non-healing of venous ulcers. The authors recommended deep debridement of all venous ulcers that were refractory to healing until the level of absence of dense fibrosis and mature collagen was achieved to allow venous ulcer healing. The conclusion of the retrospective? study<sup>10</sup> was that sharp debridement was effective in promoting healing of recalcitrant chronic venous leg ulcers. Another study on pressure ulcers reported a significant improvement of the ulcers with a spray containing Aloe vera, silver chloride and decyl glucoside (vulnoper) compared with sulike as control. As mentioned earlier (see chapter on diagnostics), the chronic wounds are colonized with bacteria, for which necrotic tissue encounter is a good nutrient medium. As a start in the treatment, removal of necrosis seems essential, considering that the removal also leads to stimulation of the formation of granular tissue and a lowering of the risk of infection<sup>1a,2</sup>.

### Conclusion

Level 3	Necrotomy reduces the level of contamination and speeds up granulation. C Falabella 1998 <sup>1a</sup> ; Blumberg 2012 <sup>1</sup> A2 Williams 2005 <sup>10</sup>
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Under cleansing, we understand the removal of necrosis, fibrin batter or other wound debris. Necrotic tissue may be surgically removed or treated with an enzymatic wound cleanser. The wound will cleanse itself via autolysis if none of these methods is chosen. An experienced physician should perform the surgical intervention in order to avoid damage to healthy tissue.

5 There are two commercial products available for an enzymatic treatment. These are fibrinolysin/pancreasdoornase (Elyase®) and collagenase (Novuxol®). It appeared from animal experimental studies by Mekkes and from investigations by Falabella that there were no indications of any positive effect on the removal of necrosis<sup>3,4</sup>. In one review, only collagenase was reported to be possibly effective<sup>5</sup>.

10 Many manufacturers claimed that the use of modern wound dressings had a positive effect on the speed of autolysis. In an investigation by Bradley et al it was reported that there was no reason for using any of these products for this purpose<sup>2</sup>.

15 A fibrin batter is often left behind after most of the necrosis has been removed. Antiseptics such as povidone-iodine, chlorhexidine, acetic acid or sodium hypochlorite/paraffin are then often chosen as the treatment of preference. In a systematic review of all the studies in this area it appeared that no conclusions could be drawn to justify the use of these, in principle, cytotoxic agents<sup>6</sup>. Cleansing with normal tap water has the same result as cleansing with an isotonic sodium solution<sup>7</sup>.

There are no known studies on the value of baths (soda or washing-powder). The moisture-absorbing effect of detergents will have an adverse effect on the wound and the surrounding area.

20 For the removal of necrotic tissue, sharp debridement is the treatment of choice<sup>1,10</sup>. This debridement can be performed using a variety of methods ranging from scalpel and curette, to more advanced methods such as high pressure hydrojet and ultrasound systems. Recently, several low pressure hydrojet systems have become available, which are highly suitable for rinsing a wound with any chosen solution, but are not as effective as high pressure hydrojet systems for the removal of debris.

25 Treatment with maggots has been known since the First World War. Maggots are excellent necrophages. A randomized, multicenter, controlled prospective trial with blinded assessment of debridement of wounds with maggots was reported by Opletalova et al<sup>8</sup>. The results showed that debridement was significantly faster only during the first week after which, another type of dressing had to be used.

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## Conclusions

Level 1	Hydrocolloids are not more effective A1: Palfreyman 2007 <sup>8</sup>
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Level 2	Surgical necrotomy is an efficient and preferred treatment. A2 Williams 2005 <sup>9</sup> Blumberg 2012 <sup>1</sup> C Falanga 2001 <sup>10</sup>
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Level 3	There are indications that collagenase is the only enzymatic agent that speeds
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	up debridement. B Bergemann 1999 <sup>5</sup>
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Level 3	It has not been demonstrated that wound dressings speed up autolysis. C Bradley 1999 <sup>2</sup>
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Level 1	Topical antiseptics are ineffective in cleansing ulcers and are, in principle, cytotoxic. A1 O'Meara 2001 <sup>11</sup>
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Level 3	Tap water cleanses as good as physiological saline. B Angeras 1992 <sup>7</sup>
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Level 3	Maggot therapy for debridement is effective only during the first week. B Opletova 2012 <sup>8</sup>
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## Recommendation 18

The working group is of the opinion that the following aspects are important when cleansing an ulcer:  
 Begin with a surgical necrotomy if possible.  
 Collagenase is the only agent for enzymatic treatment.  
 Use no topical antiseptics.  
 Cleanse wounds with tap water.

10

## 4.2 Wound dressings

### Scientific basis

Publications, among others by Winter, in which the advantages of wet treatment of wounds in comparison with “wet-gauzes” were demonstrated, already appeared towards the beginning of the 1960s. It led to faster healing. The frequently used treatment with gauzes had many disadvantages such as bleeding and pain upon removal and granular tissue damage when the dressings were changed. The necessary frequent changing also led to a disturbed healing of the wound. Therefore, products that enable the creation of a moist wound environment were introduced. An added advantage is that these products stick less to the wound bed, something that happens regularly with “wet-gauzes”.

20

Hydro gels, hydrocolloids, alginates, foam bandages and transparent foils are available for the treatment of leg ulcers. The choice of the product also depends on the level of exudation from the wound considering that each of the products has a different resorption capacity. Hydro gels, hydrocolloids and transparent foils without other applications should be used either for non-

exuding wounds or wounds that exudate a little, taking into account the fact that the chance of maceration of the edges of the wound is then high. Alginates are used when exudation is moderate to high. Foam bandages may be used in all types of exudation. No clear difference in the effectiveness, also not of traditional bandages or modern bandages was reported in medical literature. The logistical aspect favors the more modern means. An extensive review of 31 papers was not conclusive<sup>12</sup>.

The influence of antiseptic agents was reported by Kramer et al (2004)<sup>13</sup>.

### Conclusion

Level 4	There are indications that modern wound dressings are better than the traditional gauzes in the healing of wounds.  D Bradley 1999 <sup>14</sup> Bouza 2005 <sup>12</sup>
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### Other considerations

It appeared in practice that modern wound dressings offered advantages compared with traditional gauzes (moist wound environment, less pain and damage to the wound bed when dressings are changed and a lower frequency of changing the dressings). Patients prefer this. Furthermore modern wound dressings work well in combination with compression bandages and MECH.

### Recommendation 19

The working group advises modern wound dressings for achieving a moist wound environment also because the dressings do not need frequent changing. The choice of a particular product depends mainly on the level of exudation.

## 4.3 Antibacterial agents

### Scientific basis

Although ulcers as a rule are contaminated, it is useless to routinely obtain samples for culture and/or to treat them systemically with antibiotics (see also chapter on diagnostics). The use of antibiotics may lead to resistance. In a randomized study by Alinovi et al, it was observed that, when using systemic antibiotics, there was no statistically significant difference between user/non-user in healing and that there were no changes in the flora<sup>15</sup>. A sample from the wound for culture and an adequate systemic treatment based on the sensitivity spectrum is meaningful only when there are clinical indications of an extensive infection (cellulitis, erysipelas, osteomyelitis).

The topical effect of silver sulfadiazine was also looked at in various studies included in the systematic review by O'Meara et al<sup>6</sup>. Silver sulfadiazine was observed to be effective when compared with a placebo. One should take into account that prolonged use in experimental animals led to an accumulation of silver/paraffin as a cuff around the blood vessels. The extent to which this phenomenon, which is encountered in burns, also plays a role in venous leg ulcer remains unknown, but must be included in the further treatment if wound healing stagnates. Recently, many wound dressings containing a low concentration of silver for anti-bacterial effect have appeared on the market. To date, there is no evidence that wound dressings containing silver lead to faster wound healing<sup>Fehler! Textmarke nicht definiert.</sup>.

Fusidic acid is regularly prescribed as first line care. Unfortunately, no basis is found for this in medical literature. Metronidazole is particularly used on oncological ulcers against the odor

produced by the anaerobes. However, there is no indication that the use of metronidazole can lead to resistance<sup>16</sup>.

The use of topical antibiotics is not advised because of the development of resistance and contact allergy. This has been demonstrated for sofra-, genta- and neomycin.

5 Acetic acid has been used in pseudomonas-infected ulcers for a long time now. It was hereby assumed that a pseudomonas infection had an adverse effect on wound healing. An expert team of dermatologists shares this view, but evidence for this statement is lacking.

From this point of view, eradication of the pseudomonas contamination should speed up wound healing. This may be achieved practically with antibiotics effective against pseudomonas.

10 However, only one oral antibiotic family is available against pseudomonas. Resistance generally develops after several days of this monotherapy. Therefore, attempts have been made to develop other methods effective against pseudomonas infection. Acetic acid has anti-pseudomonas effect and is therefore used extensively in practice. Patients experienced painful treatment as a disadvantage. Moreover, the treatment has to be repeated several times and the effect of acetic acid on wound healing alone has not been investigated.

15 In practice, a 0.5%-1% acetic acid solution appeared to be effective. The odor produced by the bacteria generally disappeared after 3 days, which may be regarded as proof of the effectiveness.

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### Conclusions

Level 3	<i>Systemic treatment with antibiotics appeared to be meaningless in venous leg ulcers without signs of an active infection.</i> B Alinovi 1986 <sup>15</sup>
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Level 1	Siversulfadiazine/paraffin has a positive effect on wound healing A1 O Meara <sup>6</sup>
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Level 3	Topical antibiotics have no place in the treatment. B Kaye 2000 <sup>16</sup>
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Level 4	Topical 0.5%-1% acetic acid solution may be used to treat wounds contaminated with pseudomonas. However, a scientific basis is lacking for this.
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### Recommendation 20

Silver sulfadiazine/paraffin is the only eligible antimicrobial agent for topical use.

## 4.4 Skin replacement products

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### Scientific basis

Tissue-engineered skin graft products appear to be a highly promising treatment. A good and rapid healing must be achieved if this type of product adequately covers the ulcer after extensive preparation of the wound bed. In medical literature, there is only one randomized study in 120

patients by Falanga et al who reported that treatment with a skin graft was more effective after 6 months and 1 year in ulcers that had persisted for longer than a year<sup>17</sup>**Fout! Verwijzingsbron niet gevonden..Please check this!!**

5 **Conclusion**

<b>Level 3</b>	There are indications that tissue-engineered skin graft products may have a future in the treatment of venous leg ulcers.  B Falanga 1998 <sup>17</sup>
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**Recommendation 21**

Tissue-engineered skin grafts have a possible place in the future for treating venous ulcers.

10 Conventional wound dressings sometimes do not offer a satisfactory solution for treating leg ulcers. An alternative is treatment with transplanted skin (cells). There is limited indication for this here, but this is scientifically supported, with some difficulty<sup>18</sup>.  
 There are various transplantation alternatives. One can use the skin of the patient (split-skin transplantation or biopsy/Reverdin's plasty), culturing the cells from the skin of the patient  
 15 (autograft) or one can use tissue-engineered skin of donor cells (allograft).  
 There are several randomized studies in which transplantation on venous ulcers was investigated<sup>18,19,20,21,22,23,24</sup>. It can generally be stated that these studies were of moderate quality and did not always adequately prove the added value of transplantation. Poskitt and Warburg investigated split-skin transplantation<sup>19,20</sup>. The additional value of split-skin could not be proven  
 20 because of the small number of patients that was investigated.  
 It has not been proven that cultured keratinocytes (allografts) are a better choice than conventional wound dressings. There was no difference between split-skin transplantation and allograft transplantation<sup>24</sup>.  
 In a retrospective study in which ulcers were treated with biopsy transplantation (Reverdin technique) there was healing in 38% of the patients after six months<sup>25</sup>. A recurrence was observed in 27% of the patients.  
 25 Schmeller described a special technique based on the observations of Vigori that involved excision of the ulcer area and all the surrounding dermato-et liposclerosis tissue up to the healthy tissue, followed by a split-skin graft<sup>26</sup>. Of the 59 patients (76 ulcers), 79% healed in 3 months.  
 30 Unfortunately, others did not report on this technique and no randomized controlled trial is available.  
 Although widely used the value of transplantation has not been proven. In case transplantation is considered, the surgery should only take place when the majority of the ulcer bed has developed graduation tissue.

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## Conclusion

<b>Level 1</b>	The additional value of (various sorts) of transplantation in the treatment of venous ulcers has not been proven. It is possible that transplantation may speed up the healing of ulcers. Good randomized studies are necessary to prove this.  A1 Jones 2002 <sup>18</sup>
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## Other considerations

5 Nothing has been reported on the cost-effectiveness of the various ways of transplantation in relation to the conventional treatment. It can generally be assumed that this treatment will be financially unattractive if the period of healing is not evidently shorter.

## Recommendation 22

The working group is of the opinion that skin grafting may be a useful treatment on venous leg ulcer with sufficient granulation tissue.

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## ***Negative pressure treatment***

### ***Scientific basis***

15 There are still many wounds with very poor tendency to heal despite the arrival of the modern wound dressings. Negative pressure treatment (vacuum assisted closure - VAC) is used to stimulate wound healing through constant suction of wound fluid, leading to a reduction in the level of contamination, thus speeding up angiogenesis and granulation. It appeared in two small trials that VAC was superior to treatment with physiological saline-drenched gauzes<sup>27</sup>. More ref? Please check!! It has been hard to formulate useful advice because of the small numbers and methodological limitations. More randomized investigation is necessary before any scientifically-  
20 based advice can be given<sup>28</sup>.

## Conclusion

<b>Level 3</b>	In some trials, in which negative pressure treatment led to faster wound healing were of low power.  B Evans 2001 <sup>27</sup> Shirakawa 2005 <sup>28</sup>
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## **4.6 Growth factors**

### **Scientific basis**

30 The role of growth factors in wound healing is very complex. Certain growth factors (e.g. TGF-beta) play different roles in different phases of healing. To date, in spite of many years of research, only one growth factor (Becaplermin, PDGF) is registered for the treatment of diabetic foot ulcers and not for venous ulcers<sup>29</sup>.

## Conclusion

Level 3	Insufficient research has been conducted into the value of growth factors in the treatment of venous leg ulcers.  C Declair 1999 <sup>29</sup>
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## 4.7 Bed rest and hospitalization

### Scientific basis

- 5 The venous hypertension can be normalized with bed rest in long existing venous ulcers. As in supine position the ulcer is more or less at level of the heart venous pressure is below the lowest cut off point of 20 mm Hg. Most recalcitrant ulcers heal with (long) period of bed rest upon hospitalization. However, 85% recur within 2 months.<sup>30</sup>

## Conclusion

Level 3	Long bed rest is not a treatment option for venous leg ulcers <sup>30</sup> .
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## 4.8 Treatment of local pain

### Scientific basis

15 Venous ulcers can be painful. Most of the modern wound dressings claim to reduce pain. The pain is caused by the exposed nerve endings. A moist wound environment prevents dehydration and thereby reduces pain. In two trials, one with a hydrocolloid and one with a foam dressing, there was less pain when the dressings were changed and during application than with other non-adhesive dressings refs? Please check!!!. Three studies in which the use of Emla® clearly reduced the feeling of pain during the debridement in venous ulcers were reported<sup>31</sup>. More refs? Please check!!! Whether this slows down wound healing is unclear. There is no evidence that Ibuprofen dressings relieves pain<sup>32</sup>, Nelson 2010 (This reference is not in the literature list. Please Check!!!)

## Conclusion

Level 3	There are indications that pain in combined ulcers is reduced by the use of either a hydrocolloid or a foam dressing. Use of Emla cream reduces the pain caused by necrotomy.  C Briggs 2001 <sup>31</sup>
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Level 3	There is no evidence that Ibuprofen dressings relieves pain.  Briggs 2001 <sup>31</sup>
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## Literature



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## **Chapter 5 – Invasive treatment**

### **Introduction**

5 The surgical treatment of venous leg ulcers has been extensively described in medical literature and used worldwide. This treatment involves surgical intervention of the superficial venous system, the deep venous system, or the perforating venous system. A combined treatment of these three systems is also possible. Other surgical treatment for venous leg ulcers are Vigoni-Schmeller procedure by which the ulcer and all the surrounding altered skin is excised stepwise with a logical excision technique and the compartment decompression described by Hach<sup>1</sup>. However, there are no randomized controlled trials on this technique.

10 The precise pathogenesis and the role played by these three venous systems in the development of a venous leg ulcer are highly controversial. Studies of this treatment are mainly uncontrolled and are incomparable with each other. In many series, different treatments of non-uniform patient populations are presented.

15 As stated in the Scottish guidelines, there is no proof whether surgery should be chosen for treatment in case of chronic venous ulcer (an active ulcer; C6), or as secondary prevention after healing of the ulcer (C5) (CEAP-classification).

20 The Eschar study showed no difference in surgery for the superficial system before healing versus compression therapy, but a significant difference in recurrence in favor for surgery. Later on, surgery may contribute to increase the quality of life for patients with varicose veins<sup>2</sup>.

There are two randomized, controlled clinical trials indicating the role of surgery in the treatment of venous leg ulcers as compared with conservative therapy<sup>3,4</sup>.

### **25 5.1 Superficial venous system**

#### **Scientific basis**

Superficial venous insufficiency is present in about 80% of venous ulcer patients, and half of them are associated with deep incompetence, 50% of the venous leg ulcers are based on superficial incompetence only. There are no good, randomized studies on the role of isolated insufficiency of the superficial system and its surgical treatment. Good results were observed in a number of studies in which some or all of the patients received ambulatory compression therapy after the superficial system had been cleaned up surgically, which made its contribution difficult to assess.

30 In a prospective cohort study, Barwell et al reported that surgery of the superficial system in isolated insufficiency led to a lower recurrence than if no surgery had been performed<sup>5</sup>. In the same study no difference was noted between surgery and compression therapy in the healing phase. This difference between pre- and post- healing indicated a lack of compliance after healing in the compression group. Alden et al<sup>6</sup> reported a study in which minimally invasive ablation of superficial axial and perforator vein reflux led to a faster healing and a decreased recurrence when combined with compression therapy.

40 In a prospective, non-randomized study, Bello et al reported that the surgical treatment of this isolated insufficiency led to healing in most patients without additional ambulatory compression therapy<sup>6a</sup>. Scriven et al also reported the same conclusion, but in a smaller series<sup>7</sup>.

Surgical treatment of the superficial venous system consists of a crossectomy of the great saphenous vein (GSV) by stripping distally till within a handbreadth from the knee and/or a

crosssection of the small saphenous vein (SSV). Stripping of SSV is reported as highly effective for lateral leg ulcers in a study with 20 legs in which all healed after surgery within 12 weeks<sup>7,8</sup>.

## 5.2 New treatments for incompetent superficial venous study

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At present, there are new minimal invasive techniques such as the endovascular laser therapy, RF-ablation and echo-guided sclero-compression therapy (foam), which can replace classical surgery for treating varices. The first results are very promising<sup>9,10,11,12,13,14,3,4</sup>.

### 10 Conclusion

Level 2	Surgical treatment of isolated insufficiency of the superficial system in a venous leg ulcer may promote healing and reduce the recurrence rate. B Scriven 1998 <sup>15</sup> ; De Palma 1996 <sup>16</sup> C Barwell 2000 <sup>5</sup> ; Alden 2013 <sup>6</sup> ; Bello 1999 <sup>6a</sup> ; Padberg 1996 <sup>17</sup> ; Clement 1999 <sup>18</sup>
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### Recommendation 23

The working group is of the opinion that a combination of surgical treatment and ambulatory compression therapy is preferred in the case of an isolated insufficiency of the superficial system in a venous leg ulcer.

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## 5.3 Deep venous system

### Scientific basis

One can use different techniques such as valve repair, valve transposition or valve transplantation for the reconstruction of venous valve<sup>19</sup>. Raju et al reported a variation of an external valve repair technique (transcommissural valvuloplasty), whereby they concluded that this was a safe procedure with a low morbidity<sup>20</sup>. The same group also reported a study in which cryo-preserved venous valve allografts were used to treat deep venous insufficiency<sup>21</sup>. There are no good, randomized comparative studies with a prolonged follow-up period on the effect of venous valve reconstruction in the treatment of deep venous insufficiency. There has not yet been any proven effect on the healing of venous leg ulcers.

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### Conclusion

Level 3	From a pathophysiological point of view, reconstruction of venous valves would be the ideal solution in the case of deep venous insufficiency, but up till now all these techniques have only produced a valve reconstruction of limited duration, while they require extensive surgery. The effect on the healing of a venous leg ulcer has not been proven. B Dalsing 1999 <sup>21</sup> C Masuda 1994 <sup>19</sup> ; Raju 2000 <sup>20</sup>
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## 5.4 Perforator (venous) system

### Scientific basis

The role of the perforating veins (venae perforantes) in the pathogenesis of venous leg ulcers is not yet known and remains controversial. Isolated insufficiency of the perforatory system is seldom encountered in patients with a venous ulcer.

Various published series showed that surgery of incompetent perforators yielded good results in the treatment of venous leg ulcers<sup>22,23,24,25,26,27,28,29,30,31,32</sup>.

In a Dutch prospective randomized multi-center study it was observed that the ulcer-free interval improved significantly after perforator surgery in patients with a medially located and /or a recurrent venous leg ulcer<sup>33</sup>.

Treatment of insufficient perforators may be done classically (open) and endoscopically via the Subfascial Endoscopic Perforating Vein Surgery (SEPS-procedure).

The open perforantectomy according to Linton (gaiter incision) is obsolete because the chance of wound complications is unacceptable. Therefore, perforantectomies must now be done scopically<sup>30,34,35</sup>. In the long-term, the SEPS-procedure also has the same chance of healing and recurrence as the Linton-procedure, but with considerably fewer wound complications<sup>36</sup>**Fout! Verwijzingsbron niet gevonden.**Please check!!. There are also publications, which reported no difference in wound healing with or without SEPS<sup>37</sup>.

A second procedure (re-SEPS) with good results may be carried out if the SEPS procedure proves incomplete<sup>38</sup>.

### Conclusions

Level 2	The ulcer-free interval improves significantly after perforantectomy in patients with a medial and/or recurrent venous leg ulcer.  A2Van Gent 2006 <sup>33</sup>
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Level 2	The SEPS-procedure as a treatment for insufficient venae perforantes in venous leg ulcers has few wound complications, good chances of healing and a low recurrence.  The open perforantectomy according to Linton is obsolete.  A2Pierik 1997 <sup>30</sup> ; Sybrandy 2001 <sup>36</sup> B Sato 1999 <sup>34</sup> ; Stuart 1997 <sup>35</sup>
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### Other considerations

For the time being it seems that insufficient perforates in patients with a venous leg ulcer can be adequately treated. SEPS will eliminate all endoscopic visible perforates. Foam sclerotherapy can be used to treat isolated insufficient perforates .

### Recommendation 24

A perforantectomy with the SEPS-procedure should be done if an operative intervention is considered for treating venae perforates insufficiency in patients with a medial and/or a

recurrent venous leg ulcer. Isolated perforator insufficiency can be treated with foam sclerotherapy.

## 5.5 Biopsy

A biopsy from the edge of the wound may rule out the possibility of a malignancy or a malignant degeneration. It should be performed on all the (venous leg) ulcers if healing does not occur<sup>39</sup> (see diagnosis).

## 5.6 Combination of different treatments including sclero-compression therapy

### Scientific basis

Considering the fact that isolated insufficiency of venae perforantes and the deep venous system rarely occur, a combination of different surgical interventions is frequently carried out with good results<sup>16,3</sup>. There is a preference for the new endovascular ablative techniques<sup>40</sup>.

Surgical treatment of the superficial system with a GSV crosssection and stripping in combination with a perforantectomy has also yielded good results in insufficiency of the deep venous system<sup>17,30</sup>. Today, there is a preference for the new endovascular ablative techniques.

In medical literature, it has not been shown that sclero-compression therapy effectively contributes in the healing of venous leg ulcers in the case of superficial venous insufficiency. However, for the venous function it will not make a difference whether the varicose veins are treated by classical surgery, new endovascular? ablative techniques or Echo- guided foam sclerotherapy.

### Conclusions

Level 1	The treatment of combined superficial venous insufficiency and insufficiency of the venae perforantes with stripping and SEPS have good results in patients with a venous leg ulcer even when the deep venous system is insufficient.  A1 Padberg 1999 <sup>41</sup> A2 Pierik 1997 <sup>30</sup> B DePalma 1996 <sup>16</sup>
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Level 3	Sclero-compression may contribute in the effective treatment of venous leg ulcers.  D Clement 1999 <sup>18</sup> B Cabrera 2004 <sup>42</sup>
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### Recommendation 25

The treatment of first choice for patients with a venous leg ulcer with a combined insufficiency of superficial and perforatory systems is crosssection and short stripping of the GSV, as well as a perforantectomy according to the SEPS-procedure.

### Recommendation 26

The working group is of the opinion that sclero-compression therapy in the case of locally

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## Chapter 6 – Oral medication

### Scientific basis

5 Various medicines have been used to enhance the process of healing in venous ulcers. These medicines have an effect on vein diameter, edema, hematocrit, increased capillary permeability, inflammation, decreased fibrinolysis, abnormal leukocyte function and transformation of erythrocytes. . Only ergotamine has a direct influence on the vein diameter. By decreasing the vein diameter, incompetent valves can become the patent. However, the therapeutic window is small and serious risk exists for ergotism. One may generally state that oral medication without compression therapy is not useful in the treatment of venous ulcers. Oral medication as an addition to topical treatment and compression therapy is highly debated. Treatment of healthy patients with zinc did not prove to be useful<sup>1,2</sup>. Of the various medicines (aspirin and pentoxifylline) that may influence the blood flow in the microcirculation, there are only a few published studies, which in fact also report a possible influence on the duration of healing<sup>3,4,5,6,7</sup>. However, these studies are of moderate quality. In an investigation by Dale, there was no difference in the treatment with or without oral medication<sup>6</sup>. A meta-analysis supports a positive effect of Micronized purified flavonoid fraction (MPFF) treatment in combination with CT<sup>8?</sup> Please check!! It may generally be concluded that the added value of oral medication has not been proven, but pentoxifylline and aspirin have a possible additive effect<sup>7</sup>. The role of oral antibiotics in venous ulcers was already described earlier. It was reported in a review by Scallon et al<sup>9</sup> that although the overall estimated number of healed ulcers seemed to show a significant effect in favor of flavonoids [both MPFF and hydroxyethylrutosides (HR)], the results must be interpreted with caution because most of the trials were inadequately reported and thus had a risk of bias in randomization, allocation concealment, blinding and methods for addressing incomplete outcomes with a possibility of publication bias. Complaints of pain in venous ulcers are often poorly highlighted. There are no reported studies in which different means to alleviate pain have been compared. There is insufficient evidence on the role of other drugs such as Diuretics, Aspirin, Proteoglycan and MPFF.

### 30 Recommendation 27

Although ergotamine can be effective due the serious side effects, It is not recommended for daily practice.

### Conclusion

Level 1	A1 Coleridge-Smith 2005 <sup>8</sup> ; Scallon et al 2013 <sup>9</sup>
Level 2	<i>The additional value of exclusive oral medication in the treatment of venous ulcers has not been proven sufficiently.</i> A2 Jull 2002 <sup>7</sup> B Ibbotson 1995 <sup>2</sup>

### 35 Recommendation 28

The working group is of the opinion that an adequate alleviation of pain deserves attention.

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## Chapter 7 – After treatment

### Compression for the purpose of preventing recurrence of a venous leg ulcer

#### Scientific basis

5 There are no randomized studies in which compression and no compression were compared. One can only speak of indirect proof because compliance may be poor.

In systemic reviews, compression was recommended as an after-treatment for preventing recurrence,<sup>1,2,3</sup> whereby the highest pressure that the patient can tolerate is applied<sup>1</sup>, but well-adjusted to the condition of the patient<sup>2</sup>. After the venous ulcer had healed, a recurrence was  
10 observed in 32% of those wearing a class 2 stocking and in 21% of those wearing a class 3 stocking after 3-5 years<sup>4</sup>. Class 3 stockings were superior, but were tolerated less well than class 2 stockings<sup>5</sup>.

In a non-comparative clinical investigation, 53 patients in whom venous leg ulcer was closed by using an Ulcercare® bandage stocking system (10-15 mm Hg understocking + a 30 mm Hg stocking with a zip) were treated with the same stockings after the ulcer was healed<sup>3</sup>. In the group  
15 that wore stockings (almost one-half) only 4% developed a recurrent ulcer after 6 months, whereas 79% of those who did not or only occasionally wore the stockings developed a recurrent ulcer.

In another study, 188 patients with recently closed ulcers were mostly prescribed ready-made class 2 MECH. A recurrent ulcer was observed in 26% of the patients after 1 year and in 31% of  
20 the patients after 1.5 years. A risk factor, among others, was not wearing the MECH. Ref? please check!!!

In most cases it will be decided to prescribe MECH as an after treatment. It is important to pre-select the correct type of MECH for the patient. A program of requirements, which supports making a correct decision has been compiled for this purpose<sup>6</sup>.

25 The prophylactic use of compression therapy in patients with previous venous ulcers was clearly shown to be cost-effective. This meant that it is much cheaper to prescribe adequate MECH after ulcers have healed than to cure recurrent ulcers<sup>7</sup>.

#### Conclusion

Level 2	Compression therapy should be given after a venous leg ulcer has healed. Compression with high-pressure MECH (class 3) is better for preventing recurrence than with low-pressure MECH (class 2), but is tolerated less well.
	A1 Nelson 2001 <sup>1</sup> ; Agus 2001a <sup>2</sup> ; NZGG 1999 <sup>3</sup> ; Agus 2001b <sup>4</sup>

#### Recommendation 29

30 Compression therapy with Medical Elastic Compression Hosiery (MECH), which exerts high pressure and high stiffness, should be prescribed to prevent recurrence after a venous leg ulcer has healed.

### 7.2 Ablation of superficial refluxes for preventing the recurrence of a venous leg ulcer

#### Scientific basis

35 When the venous ulcer has epithelialized after conservative therapy, the patient is not cured because the pathophysiological background that led to ulceration is still present. This fact explains

the high recurrence rate ranging between 26-69% in 12 months. Ablation of venous refluxes by using surgery or endovenous techniques may normalize the disturbed venous hemodynamics and prevent ulcer recurrence.

5 It has been shown that most patients with chronic venous ulcers will benefit from simple venous surgery in addition to conventional compression treatment in an effort to reduce the recurrence of ulcers within 12 months<sup>8</sup>.

Level 2	Ablation of refluxes in the great saphenous vein by surgery reduces the recurrence of ulcers within 12 months.  A2 Barwell 2004 <sup>8</sup> ; Alden et al 2013 <sup>9</sup>
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### Recommendation 30

Ablation of superficial refluxes by surgery, by endovenous methods or by (foam-) sclerotherapy should be considered in all cases.

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## **Chapter 8 – Life style**

### **Introduction**

5 In this chapter, the importance of advice on the life style of the patients during the treatment and the aftercare phase of leg ulcer is discussed. A review of studies on this subject is first given. In the second paragraph a number of examples taken from practice are presented.

### **8.1 Life style in medical literature**

#### **Scientific basis**

10 Little proof of the influence of life style on the prevention and healing of leg ulcers is encountered in the medical literature. In their publication, Kunimoto et al presented 12 recommendations, which stated the best clinical interventions and expert opinion supplemented by available investigation. There was one recommendation that was directly related to the life style of the patient, namely  
15 “consultation with revalidation experts to maximize activity and mobility”. Limitation in the movement of the ankle leads to an increase in the venous pressure and development of an edema in patients with chronic venous insufficiency. Walking improves the calf muscle pump function<sup>1</sup>.

The nutritional status of patients with leg- and foot ulcers was evaluated in relation to social demographic factors such as mobility, physical activity, ulcer history and problems related to the ulcer. In 51% of the cases there was venous insufficiency, in 9% of the cases there was an arterial  
20 insufficiency and in 11% of the cases there was a combined venous-arterial insufficiency. The remaining 29% of the causes could be ascribed to afflictions such as diabetes, trauma or others. The patients (20 men and 50 women) lived alone and received a first line treatment. The “Mini Nutritional Assessment” (MNA) was used to establish the nutritional status. According to the MNA, 32 patients ran the risk of malnutrition and two of them were malnourished. The patients who were  
25 at risk generally lived alone and depended more on help (aids) from mobility and home care organizations than those who were well-fed. There were no significant differences between the number and the duration of open ulcers in well-fed patients and those who were at risk of malnutrition. This investigation showed that the risk of malnutrition was a general problem among these 70 elderly patients with leg- and foot ulcers<sup>2</sup>. Lazareth et al<sup>2a</sup> investigated smoking and  
30 Vitamin C levels in patients with leg ulcers. These patients were frequent smokers and their Vitamin C levels were significantly lower. There is now evidence that this also influences the healing process.

The healing of ulcers, the recurrence of ulcers, the nutritional status and the living conditions of the elderly patients with leg ulcers were investigated in a subsequent study. Of the 70 patients who  
35 were involved in the investigation in 1999, 61% were still alive in 2000 and 88% of these participated in the follow-up study. The ulcers had healed in 50% of the patients, amputation had been necessary in 5% and open ulcers were still present in 45% (in 6 of the patients, the previous ulcers had not yet healed and new ulcers had again developed in 11 elderly patients). The average MNA scores were lowered as were the average ADL scores and mobility in the patients with open  
40 ulcers, but not among the patients whose ulcers had healed. The patients with healed ulcers had higher average scores on social interaction than those with open ulcers and the average scores on the quality of the surroundings were significantly higher. The results showed that there was a possible relationship between nutrition and the living conditions and the healing of leg ulcers<sup>3</sup>.

45 The aim of the study by Wipke-Travis et al was to investigate the nutrition, the tissue oxygen and the healing of venous leg ulcers. The nutrition status, the physical dimensions, the biochemical

indices, the two three-day diet reports and the level of tissue oxygen from the 25 participating individuals were recorded. The results of this study showed that there were no statistically significant relationships between the biochemical nutrition indices, tissue oxygen and healing<sup>4</sup>.

The prevalence of malnutrition was high in patients suffering from leg ulcers. The nutritional status may be a marker of wound tendency and a risk factor for delayed wound healing<sup>5</sup>.

### Conclusion

Level 3	There is a possible relationship between nutrition, living conditions and the healing of leg ulcer.  <i>C Wissing 1999<sup>2</sup>; 2001<sup>3</sup></i>
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### Recommendation 31

An adequate patient care in the treatment of venous leg ulcers also includes optimization of the nutritional status.

## 8.2 Information and advice

In 1985, a project was started in the Amsterdam region with the aim of improving the quality and/or reducing the costs, whereby it was looked at whether it was possible to bring about a change in the existing care and treatment patterns for disorders, which required a prolonged stay in the hospital.

The results of the project were used to develop a care protocol. Leg ulcers were selected as one of the disorders. A first protocol was ready in 1987. An update followed in 2000<sup>6</sup>. Considerable attention was paid to information and advice on life style in this protocol.

In any case the patient should receive information on:

Causes of the ulcer

Treatments

The necessity to treat other underlying diseases

Advice must also be given on:

The necessity of regular movement of the foot and the leg

Well-fitting footwear

Skin and nail care

It also emerged from other experiments in the Netherlands that providing information on the treatment of "open ulcers" was an important issue. The advice, which corroborates the advice in the Amsterdam protocol (protocols of the Foundation for Transmural care The Hague e.o., Medical Center Molendael, Baarn, Lorentz Hospital, Zeist, Home care program of KITZ, Groningen) is cited in the various care booklets.

Providing information and advice is also high on the international agenda. It was once again emphasized in investigations by Seiter et al that movement was very important in the treatment of chronic venous insufficiency<sup>7</sup>. In their study, Blair et al mentioned various risk factors including overweight, inactivity, the use of walking aids and reduced ankle movement in the development of new ulcers<sup>8</sup>.

Evaluation of whether the advice and counselling provided is followed leads to a better compliance with the therapy.

## Conclusion

Level 4	Adequate information and advice on life style provide an important contribution in the prevention and the treatment of venous leg ulcers.  <i>D Hulsebosch 1993<sup>6</sup>; Seiter 2001<sup>7</sup>; Blair 2001<sup>8</sup></i>
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## Recommendation 32

The working group is of the opinion that providing information and advice concerning life style is indispensable in the treatment of leg ulcers.

Attention must at least be paid to the following points:

Avoiding immobility

Encouraging the use of the calf muscle pump (walking, adequate footwear)

Avoiding (developing) overweight

Encouraging adequate nutrition

Discouraging smoking

## 5 Literature

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**Conflicts of interests**

The Work Under Consideration for Publication					
		<b>Hugo Partsch</b>	<b>Cornu-Thenard</b>	<b>Martino Neumann</b>	<b>Markus Streit</b>
1	Grant	no	NO	no	no
2	Consulting fee or honorarium	no	NO	no	no
3	Support for travel to meetings for the study or other purposes		NO	no	no
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no	NO	no	no
5	Payment for writing or reviewing the manuscript	no	NO	no	no
6	Provision of writing assistance, medicines, equipment, or administrative support	no	NO	no	no
7	Other	no	NO	no	no

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	-	NO	no	no
2	Consultancy	Tactile USA	NO	no	no
3	Employment	-	NO	no	no
4	Expert testimony	-	NO	no	no
5	Grants/grants pending	-	NO	no	no
6	Payment for lectures including service on speakers bureaus	-	NO	no	no
7	Payment for manuscript preparation	-	NO	no	no

8	Patents (planned, pending or issued)	-	NO	no	no
9	Royalties	-	Yes for Extensor	no	no
10	Payment for development of educational presentations	-	No	no	no
11	Stock/stock options	-	No	no	no
12	Travel/accommodations/meeting expenses unrelated to activities listed**	-	No	Medi GmbH	no
13	Other (err on the side of full disclosure)	-	No	no	no

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no	NO	no	no

**Conflicts of interests Eberhard Rabe**

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	European College of Phelbology			
2	Consultancy	Sigvaris			
3	Employment	University of Bonn, Germany			
4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	no			
7	Payment for manuscript preparation	no			

8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	Kreussler, Medi			
13	Other (err on the side of full disclosure)	no			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			

## Conflicts of interests

The Work Under Consideration for Publication					
		Giovanni Mosti	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other				

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	no			
2	Consultancy	no			
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	no			
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			

10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	no			
13	Other (err on the side of full disclosure)	no			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no			



## Conflicts of interests

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	no			
2	Consulting fee or honorarium	no			
3	Support for travel to meetings for the study or other purposes	no			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	no			
5	Payment for writing or reviewing the manuscript	no			
6	Provision of writing assistance, medicines, equipment, or administrative support	no			
7	Other	no			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	KDS			
2	Consultancy	no			
3	Employment	no			
4	Expert testimony	no			
5	Grants/grants pending	no			
6	Payment for lectures including service on speakers bureaus	no			
7	Payment for manuscript preparation	no			
8	Patents (planned, pending or issued)	no			
9	Royalties	no			
10	Payment for development of educational presentations	no			
11	Stock/stock options	no			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	no			
13	Other (err on the side of full disclosure)	no			



\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships				
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	no		

I have no conflicts of interest at all.

Rhoon 20-12-2014 *Leif Huse*

Conflicts of interests

MICHAEL JÜNGER

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant	<input checked="" type="checkbox"/>			
2	Consulting fee or honorarium	<input checked="" type="checkbox"/>			
3	Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>			
5	Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>			
6	Provision of writing assistance, medicines, equipment, or administrative support	<input checked="" type="checkbox"/>			
7	Other				

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	<input checked="" type="checkbox"/>			
2	Consultancy	<input checked="" type="checkbox"/>			
3	Employment	<input checked="" type="checkbox"/>			
4	Expert testimony	<input checked="" type="checkbox"/>			
5	Grants/grants pending	<input checked="" type="checkbox"/>			
6	Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>			
7	Payment for manuscript preparation	<input checked="" type="checkbox"/>			
8	Patents (planned, pending or issued)	<input checked="" type="checkbox"/>			
9	Royalties	<input checked="" type="checkbox"/>			
10	Payment for development of educational presentations	<input checked="" type="checkbox"/>			
11	Stock/stock options	<input checked="" type="checkbox"/>			
12	Travel/accommodations/meeting expenses unrelated to activities listed**	<input checked="" type="checkbox"/>			
13	Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>			

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?				

October 21<sup>st</sup> 2014

Dr. Jünger

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# RATTLE AA

## Conflicts of interests

The Work Under Consideration for Publication					
		Name	Name	Name	Name
1	Grant				
2	Consulting fee or honorarium	/			
3	Support for travel to meetings for the study or other purposes	/			
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	/			
5	Payment for writing or reviewing the manuscript	/			
6	Provision of writing assistance, medicines, equipment, or administrative support	/			
7	Other	/			

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership				
2	Consultancy				
3	Employment				
4	Expert testimony				
5	Grants/grants pending				
6	Payment for lectures including service on speakers bureaus				
7	Payment for manuscript preparation				
8	Patents (planned, pending or issued)				
9	Royalties				
10	Payment for development of educational presentations				
11	Stock/stock options				
12	Travel/accommodations/meeting expenses unrelated to activities listed**				
13	Other (err on the side of full disclosure)				

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships				
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?			

No conflict

for the above  
20.10.14