

# CONSENSUS

## Society for Vascular Surgery and American Venous Forum Guidelines on the management of venous leg ulcers: the point of view of the International Union of Phlebology

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## Preface

When I became President of the UIP, among my main goals was to establish some consensus or guidelines for some very important or frequently-seen pathological situations in Phlebology. One such topic was “venous ulcers”.

Venous leg ulcers are a very common disease that predominantly affects the humblest people on lower income and causes great physical, social and financial suffering.

Although this disease has been described since antiquity, until today we have been unable to reach a consensus on the best way to treat this painful pathological condition. This is the reason why this document is not a consensus but a set of guidelines and best practice recommendations.

An old medical proverb says that when there are multiple ways to treat the same disease it is often because none of the methods is very good. Indeed, venous ulcer fits perfectly into this category. There are many suggested ways to treat a venous ulcer and there is no unanimity among the experts.

In order to prepare this document before the end of my presidency it was important to choose a motivated coordinator with world-renowned capacity. After several contacts and counseling of the most distinguished experts in the world, it was decided to invite Dr. Giovanni Mosti for this herculean task. Giovanni accepted the challenge and started to work immediately. He quickly determined the main points to be discussed and

convened a virtual group of experts to contribute and to discuss the topic.

After a few months of work, we received a letter from the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) informing us that, after some years of work, they had developed a set of guidelines about venous ulcers, and were requesting the endorsement of the UIP before publication.

In a meeting with Dr. Mosti, we thought there was no reason to repeat what had already been done and that the UIP would endorse the document. However, being the UIP an international society, we carried on a reviewing process taking into account aspects arising from different geographic realities.

So Dr. Mosti continued with his work collecting the comments and suggestions of several authors from around the world.

This document is the final result of all this effort by Dr. Mosti and the group of authors. The SVS-AVF document served as a model to which some comments and suggestions were added, mainly by doctors from Europe and other parts of the world such as South America.

I would like to thank all those who contributed to this document. You have brought great prestige to Phlebology and the UIP.

ANGELO SCUDERI  
*President of UIP*

## Introduction

Clinical guidelines consist of evidence-based recommendations designed to help clinicians and patients in making decisions about appropriate health care for specific circumstances.

Preparing clinical guidelines implies enormous effort as it is necessary to check if evidence exists and how strong it is in looking for pathophysiology, formulating a diagnosis, making a prognosis, predicting outcomes, and choosing the best treatments considering not only the benefits but also the risks, costs and possible alternative treatments.

The value of a guidelines document is that it provides recommendations resulting in the best quality of care and the most effective treatments with an eye to cost-saving.

In Phlebology one of the most important topics is venous leg ulcers (VLUs).

VLUs have a prevalence of 1% to 1.5% in the general population (but 5% over 80 years old)<sup>1-4</sup> and can be extremely long-lasting (about 20% do not heal after 2 years, and about 8% do not heal after 5 years).<sup>5,6</sup> VLUs are often the cause of unwanted clinical effects such as pain, infections, malodor and important socioeconomic consequences including prolonged disability and compromised work ability. Finally, VLUs have an amazingly variable economic impact depending on, among other factors, the quality of care.<sup>7</sup>

For this reason, producing guidelines for VLUs which could provide evidence-based recommendations to increase the quality and effectiveness of care, minimize costs, and have worldwide validity was the primary goal of the International Union of Phlebology (UIP). To achieve this goal, the UIP invited a group of international experts in the field of VLUs to be involved in the preparation of the guidelines, with Giovanni Mosti as Chair. This UIP Committee started working when the final version of "Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum"<sup>8</sup> was nearing publication.

The Chairs of the "SVS-AVF Joint Clinical Practice Guidelines Committee - Venous Leg Ulcer" contacted the UIP President providing him with their document and asking for the endorsement of the UIP.

The document was made available to the UIP

Committee which then decided to revise its original project, shifting from the creation of a totally new guidelines document, maybe very similar to the SVS-AVF one, to the endorsement of the SVS-AVF guidelines. The dedicated UIP Committee, at the same time, took this opportunity to provide suggestions, comments and proposals for changes that might be valid for future common guidelines updating.

The aim of the present paper was to report the UIP Committee's comments/implementations for the SVS-AVF guidelines on VLU.

In order to reach this goal, the UIP Committee was divided into different sub-committees, each dedicated to commenting on one of the eight sections of the SVS-AVF guidelines as reported above. Comments and proposals for changes were sent to the Chair of the Committee, who prepared a first draft after collecting all the comments and recommendations. This first draft was then sent to the entire group to obtain general agreement on the whole document, and subsequently the final draft was prepared.

## Results

In this section the cited guideline numbers cited refer to the published SVS-AVF guidelines.<sup>8</sup>

### Ulcer definition

In guideline 1.1 venous ulcer definition is reported as:

"We suggest use of a standard definition of venous ulcer as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension. [BEST PRACTICE]"

WE SUGGEST CHANGING GUIDELINE 1.1 TO:

*We suggest use of a standard definition of venous ulcer as an open skin lesion of the leg or foot, that shows little or no tendency to spontaneous healing and occurs in an area affected by ambulatory venous hypertension and showing other signs of chronic venous insufficiency. [BEST PRACTICE]*

Comment: The concomitance of chronic venous disease (CVD), such as varicose veins and post-thrombotic syndrome (PTS), with leg ulcers of other origin is very high because CVD is very common (approx. 25-30% in the general population). As per the definition proposed by SVS-

AVF, a drug-induced (hydroxyurea) ulcer or even a pyoderma gangrenosum in the ankle region would fulfil the definition of a venous ulcer, with or without the concomitant presence of varicose veins or of post-thrombotic changes. Venous ulcers, however, do not appear in normal skin but have a history of previous skin changes in the same area with pigmentation, lipodermatosclerosis or white atrophy. The venous ulcer develops within the area of these skin changes as a decompensation from impaired microcirculation.

## Venous anatomy and pathophysiology

Regarding venous anatomy, guideline 2.1 reports:

“We recommend use of the International Consensus Committee on Venous Anatomical Terminology for standardized venous anatomy nomenclature. [BEST PRACTICE]”.

WE AGREE AND SUGGEST A MODIFICATION OF THE GUIDELINE EXPLANATION:

Comment: A clear-cut discrimination between saphenous trunks, including the great saphenous vein (GSV), the small saphenous vein (SSV), the anterior accessory saphenous vein (AASV), the posterior accessory saphenous vein (PASV) and Giacomini vein, on the one hand, and tributaries on the other hand is missing. The CEAP classification<sup>9</sup> clearly discriminates between reflux in the saphenous trunks ( $P_{r2,3,4}$ ) and reflux in tributaries ( $P_{r5}$ ). This seems to be clinically relevant, because the treatment of saphenous trunks is different (thermal or chemical ablation, interruption or stripping) from treatment of tributaries (phlebectomies or foam sclerotherapy).

We propose to refine the paragraph with the explanation discriminating saphenous trunks and tributaries according to their different relationships with the saphenous compartment: saphenous trunks are situated in the saphenous compartment (between the saphenous and the muscular fascia) and tributaries are situated outside the saphenous compartment (between the saphenous fascia and the skin).<sup>10</sup>

Regarding pathophysiology of VLU guideline 2.2 reports:

“We recommend a basic practical knowledge of venous physiology and venous leg ulcer patho-

physiology for all practitioners caring for venous leg ulcers. [BEST PRACTICE]”.

WE AGREE. HOWEVER WE WOULD LIKE TO UPDATE THE GUIDELINE EXPLANATION:

Comment: The reviews recently published on Proteomics and Degradomics of wound leg ulcer fluids<sup>11, 12</sup> highlight the differences in biomolecular composition of ulcer fluids, leading to better knowledge of biochemical pathways involved in both inflammatory and proteolytic processes, especially regarding the inflammatory and granulating steps of ulcer healing. These mechanisms will set the basis for the identification of biomarkers for more effective therapeutic approaches.<sup>11, 12</sup>

## Clinical evaluation

Regarding laboratory evaluation, the guideline 3.6 reports:

“We suggest laboratory evaluation for thrombophilia for patients with a history of recurrent venous thrombosis and chronic recurrent venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 3.6 TO:

*We suggest against routine laboratory evaluation for thrombophilia for patients with chronic recurrent venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: Recurrent DVT is the most important risk factor for developing PTS and continuous anticoagulation is recommended by ACCP guidelines.<sup>13</sup> Laboratory testing does not add much useful information for clinical practice.

Regarding venous disease classification, guideline 3.12 reports:

“We recommend that all patients with venous leg ulcer be classified on the basis of venous disease classification assessment, including clinical CEAP, revised Venous Clinical Severity Score, and venous disease-specific quality of life assessment. [BEST PRACTICE]”.

WE PROPOSE TO CHANGE GUIDELINE 3.12 TO:

*We suggest that all patients with venous leg ulcer should be classified according to the advanced CEAP classification. Assessment by revised ve-*

nous clinical severity scoring (VCSS), and venous disease-specific quality of life (QOL) are recommended for more complete documentation [BEST PRACTICE

Comment: Not only the use of the 'C' in CEAP classification, but also that of the whole advanced CEAP classification<sup>9</sup> helps to understand what kind of venous ulcer is present. 'E', etiology: primary or secondary (post-thrombotic) origin? 'A', anatomy: which veins are involved? 'P', pathophysiology: only reflux, or obstruction, or both?

The VCSS<sup>14</sup> helps to understand the severity of the disease as does QOL, and both are ideal tools for comparison between before and after treatment. However, these tools have little impact on the choice of the therapeutic option.

We think that "We suggest" is more appropriate than "We recommend" (we only have Best Practice).

#### Regarding venous procedural outcome assessment, guideline 3.13 reports:

"We recommend venous procedural outcome assessment including reporting of anatomic success, venous hemodynamic success, procedure-related minor and major complications, and impact on venous leg ulcer healing. [BEST PRACTICE]"

WE PROPOSE TO CHANGE GUIDELINE 3.13 TO:

*We suggest venous procedural outcome assessment including reporting of clinical success (healing rate, recurrence rate), anatomic success, venous hemodynamic success, procedure-related minor and major complications [BEST PRACTICE]*

Comment: Most important are the healing and recurrence rates. They should be the main outcome of any procedure. Anatomic and hemodynamic outcomes as well as complications are secondary outcomes.

We think that "We suggest" is more appropriate than "We recommend" (we only have Best Practice).

## Wound care

#### Regarding biologic debridement, guideline 4.8 reports:

"We suggest that larval therapy for venous leg ulcers can be used as an alternative to sur-

gical debridement. [GRADE 2; LEVEL OF EVIDENCE B]"

WE PROPOSE TO CHANGE GUIDELINE 4.8 TO:

*We suggest larval therapy for venous leg ulcers, when available, to be used as an alternative to surgical debridement [GRADE 2; LEVEL OF EVIDENCE B]*

Comment: Larval therapy is available only in a very restricted number of countries.

WE PROPOSE TO ADD A NEW GUIDELINE REGARDING AUTOLYTIC DEBRIDEMENT:

#### Guideline 4.8a: Autolytic debridement

*We suggest the use of autolytic debridement by moist wound dressings, alone or in combination, to promote wound healing in keeping with guideline 4.14. [GRADE 2; LEVEL OF EVIDENCE B]*

Comment: The process occurs to some extent in all wounds when the body attempts to shed devitalized tissue when the body attempts to shed devitalized tissue by the use of moisture which naturally rehydrates, softens, degrades and sloughs the necrotic tissue, exposing good underlying tissue. Autolytic debridement by specific wound dressing is selective as only necrotic tissue is liquefied. The presence of wound enzymes such as matrix metalloproteinases (MMPs) facilitates this process.<sup>15</sup> Such treatment requires special management of the moisture balance using moisture-donating or moisture-absorbing dressings.<sup>16, 17</sup>

#### Guideline 4.13 "Topical antibiotics for infected wounds" and 4.15 "Topical dressings containing antimicrobials":

"We suggest against the use of topical antimicrobial agents for the treatment of infected venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE C]"

and

"We recommend against the routine use of topical antimicrobial-containing dressings in the treatment of non-infected venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE A]"

WE PROPOSE SEMANTIC CHANGES TO:

*We suggest against using topical antibiotic agents for the treatment of infected venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE C]*

and

*We suggest against the routine use of topical antiseptic-containing dressings in the treatment*

of non-infected venous leg ulcers. [BEST PRACTICE]

Comment: Antimicrobials is a term that can include antibiotics in addition to antiseptics.

For 4.15 we think that “We suggest” is more appropriate than “We recommend” (we only have Best Practice).

Regarding periulcer skin management, guideline 4.16 reports:

“We suggest application of skin lubricants underneath compression to reduce dermatitis that commonly affects periulcer skin. [GRADE 2; LEVEL OF EVIDENCE C] In severe cases of dermatitis associated with venous leg ulcers, we suggest topical steroids to reduce the development of secondary ulcerations and to reduce the symptoms of dermatitis. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE A SEMANTIC CHANGE TO:

*We suggest application of protective skin barrier substances underneath compression in order to reduce dermatitis that commonly affects periulcer skin. [GRADE 2; LEVEL OF EVIDENCE C] In severe cases of dermatitis associated with venous leg ulcers, we suggest the temporary use of topical steroids to reduce the development of secondary ulcerations and to reduce the symptoms of skin irritation. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: The term “protective skin barrier substances” seems to be more appropriate than “skin lubricant”.

Regarding split-thickness skin grafting, guideline 4.19 reports:

“We suggest against split-thickness skin grafting as primary therapy in treatment of venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE B]. We suggest split-thickness skin grafting with continued compression for selected large venous leg ulcers that have failed to show signs of healing with standard care for 4 to 6 weeks. [GRADE 2; LEVEL OF EVIDENCE B]”.

WE PROPOSE TO CHANGE GUIDELINE 4.19 TO:

*We suggest against split-thickness skin grafting as primary therapy in treatment of venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE B] We suggest split-thickness skin grafting with*

*correction of underlying disease and continued compression for selected large venous leg ulcers that have failed to show signs of healing with standard care for 4-6 weeks. [GRADE 2; LEVEL OF EVIDENCE B] We recommend, prior to split-thickness skin grafting, leg decongestion by compression therapy and adequate wound bed preparation including complete removal of slough, debris and any necrotic tissue. [GRADE 1; LEVEL OF EVIDENCE C] We recommend additional evaluation and management of increased bio-burden levels prior to the application of split-thickness skin grafting. [GRADE 1; LEVEL OF EVIDENCE C]*

Comment: We need to take into account that sharp debridement and grafting combined with correction of underlying disease and compression may achieve excellent healing rates in hard-to-heal ulcers. Ulcer bed must be adequately prepared and bio-burden reduced to a minimum before grafting procedures. Simultaneous correction of underlying pathology promotes healing and prevents recurrences.<sup>18-20</sup>

Regarding cellular therapy, preparation for cellular therapy, frequency of cellular therapy application, tissue matrices, human tissues or other skin substitutes (guidelines from 4.20 to 4.23)

Guideline 4.20: Cellular therapy

“We suggest the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) to increase the chances for healing in patients with difficult-to-heal venous leg ulcers in addition to compression therapy in patients who have failed to show signs of healing after standard therapy for 4 to 6 weeks. [GRADE 2; LEVEL OF EVIDENCE A]”

Guideline 4.21: Preparation for cellular therapy

“We suggest a therapeutic trial of appropriate compression and wound bed moisture control before application of cellular therapy. [GRADE 2; LEVEL OF EVIDENCE C] We recommend that adequate wound bed preparation, including complete removal of slough, debris, and any necrotic tissue, be completed before the application of a bilayered cellular graft. [GRADE 1; LEVEL OF EVIDENCE C] We recommend additional evalu-

ation and management of increased bioburden levels before the application of cellular therapy. [GRADE 1; LEVEL OF EVIDENCE C]”

**Guideline 4.22: Frequency of cellular therapy application**

“We suggest reapplication of cellular therapy as long as the venous leg ulcer continues to respond on the basis of wound documentation. [GRADE 2; LEVEL OF EVIDENCE C]”

**Guideline 4.23: Tissue matrices, human tissues, or other skin substitutes**

“We suggest the use of a porcine small intestinal submucosal tissue construct in addition to compression therapy for the treatment of venous leg ulcers that have failed to show signs of healing after standard therapy for 4 to 6 weeks. [GRADE 2; LEVEL OF EVIDENCE B]”

WE PROPOSE TO SUMMARIZE THE PREVIOUS FOUR GUIDELINES IN ONE GUIDELINE – 4.20: SKIN SUBSTITUTES

*We suggest the use of skin substitutes, including among others cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers), porcine small intestinal submucosal tissue construct, acellular dermal substitutes, cadaveric skin (when available), in addition to correction of underlying disease and continued compression therapy. This ulcer bed preparation may act as a prelude to additional skin grafting procedures in very extensive (circumferential), deep (because of significant tissue loss), long standing, venous leg ulcers that failed to show signs of healing after standard therapy for 4 to 6 weeks. We suggest against routine use of skin substitutes. [GRADE 2; LEVEL OF EVIDENCE C] We recommend that, prior to skin substitute use, adequate wound bed preparation and moisture control be completed including complete removal of slough, debris and any necrotic tissue. [GRADE 1; LEVEL OF EVIDENCE C] We recommend additional evaluation and management of increased bio-burden levels prior to the application of cellular therapy. [GRADE 1; LEVEL OF EVIDENCE C]*

Comment: Cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers), porcine small intestinal submucosal tissue construct, acellular dermal substitutes, ca-

daveric skin are used in a very restricted number of countries. Many of them are extremely expensive and seem not to add any additional beneficial effect to the split-thickness skin grafting although randomized controlled studies are required.

The split-thickness skin grafting is a quick and cheap procedure and severe complications regarding the donor site are unknown. The original use of tissue engineered skin substitutes and cultured skin cells in burn injuries in patients with insufficient autologous skin for grafting, does not necessarily apply to venous ulcers. Their use must be restricted to the clinical situations mentioned above.<sup>21-30</sup>

**Compression**

WE PROPOSE TO ADD A NEW GUIDELINE

**Guideline 5.1a: Compression pressure – Ulcer healing**

*In a patient with a venous leg ulcer without arterial involvement or peripheral neuropathy, we recommend strong compression pressure (>40 mmHg resting pressure at the ankle) over low compression pressure to increase venous leg ulcer healing rate. [GRADE 1; LEVEL OF EVIDENCE B]*

Comment: We have evidence that strong compression is more effective than low compression in promoting ulcer healing. Compression is defined as strong when the exerted pressure is higher than 40 mmHg and low when the pressure is lower than 20 mmHg.<sup>31-35</sup>

**Regarding Compression – Ulcer recurrence, guideline 5.2 reports:**

“In a patient with a healed venous leg ulcer, we suggest compression therapy to decrease the risk of ulcer recurrence. [GRADE 2; LEVEL OF EVIDENCE B]”.

WE PROPOSE TO CHANGE GUIDELINE 5.2 TO:

*In a patient with a healed venous leg ulcer, we recommend compression therapy to decrease the risk of ulcer recurrence. [GRADE 1; LEVEL OF EVIDENCE B].*

Comment: Two RCTs<sup>36, 37</sup> and one large observational study agree on the effectiveness of stockings in ulcer recurrence prevention;<sup>38</sup> maybe trials have some flaws but the evidence, is strong.



Increasing the level of evidence, we think that “We recommend” is more appropriate than “We suggest”.

The old reference 289 could be replaced by a new reference,<sup>39</sup> supporting a higher level of evidence.

Regarding intermittent pneumatic compression, guideline 5.5 reports:

“We suggest use of intermittent pneumatic compression when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 5.5 TO:

*We suggest using intermittent pneumatic compression (IPC) when other compression options are not available, cannot be used, or have failed to aid in venous leg ulcer healing after prolonged compression therapy. [GRADE 2; LEVEL OF EVIDENCE C]*

*We suggest IPC in addition to standard compression when possible. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: There is evidence from clinical studies that IPC used in addition to standard compression might improve healing of venous ulcers.<sup>40, 41</sup>

**Operative/endovascular management**

Regarding superficial venous reflux and active venous leg ulcer, guideline 6.1 reports:

“In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we suggest ablation of the incompetent veins in addition to standard compressive therapy to improve ulcer healing. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 6.1 TO:

*In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux directed to the bed of the ulcer, we suggest surgery of the incompetent veins, or alternative ablation techniques, in addition to standard compressive therapy to improve ulcer healing. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: The word “ablation” is usually used together with endovenous techniques that are the least documented, although the word in reality also includes open surgical techniques like high ligation and stripping. That is why endovenous techniques are named as alternative ablative techniques in this document. There is no scientific evidence showing that endovenous thermal, or non-thermal ablation is effective in promoting VLU healing<sup>42, 43</sup> but there is some evidence for open surgery (high ligation/stripping).<sup>44-47</sup>

We also suggest to erase the term “axial” from guidelines 6.1 to 6.4 as an alternative course of reflux (e.g., medial ulcer due to SSV incompetence or lateral ulcer due to GSV incompetence) must also be taken into account.<sup>48</sup>

Regarding superficial venous reflux and active venous leg ulcer, guideline 6.2 reports:

“In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we recommend ablation of the incompetent veins in addition to standard compressive therapy to prevent recurrence. [GRADE 1; LEVEL OF EVIDENCE B]”.

WE PROPOSE TO CHANGE GUIDELINE 6.2 TO:

*In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux directed to the bed of the ulcer, we recommend surgery [GRADE 1; LEVEL OF EVIDENCE B] or an alternative ablation technique [GRADE 2; LEVEL OF EVIDENCE C] of the incompetent veins in addition to standard compressive therapy to prevent recurrence.*

Comment: The effectiveness of prevention of ulcer recurrence has only been shown for open surgery.<sup>47, 49, 50</sup> Regarding ablation the evidence level is, so far, only worthy of 2C.<sup>42, 43</sup>

Regarding superficial venous reflux and healed venous leg ulcer, guideline 6.3 reports:

“In a patient with a healed venous leg ulcer (C5) and incompetent superficial veins that have axial reflux directed to the bed of the ulcer, we recommend ablation of the incompetent veins in addition to standard compressive therapy to prevent recurrence. [GRADE 1; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 6.3 TO:

*In a patient with a healed venous leg ulcer (C5) and incompetent superficial veins that have reflux directed to the healed ulcer area, we recommend surgery [GRADE 1; LEVEL OF EVIDENCE B] or an alternative ablation technique [GRADE 2; LEVEL OF EVIDENCE C] of the incompetent veins in addition to standard compressive therapy to prevent recurrence.*

Comment: See comments for guideline 6.2.

Regarding superficial venous reflux with skin changes at risk for venous leg ulcer (C4b), guideline 6.4 reports:

*“In a patient with skin changes at risk for venous leg ulcer (C4b) and incompetent superficial veins that have axial reflux directed to the bed of the affected skin, we suggest ablation of the incompetent superficial veins in addition to standard compressive therapy to prevent ulceration. [GRADE 2; LEVEL OF EVIDENCE C]”.*

WE PROPOSE TO CHANGE GUIDELINE 6.4 TO:

*In a patient with skin changes at risk for venous leg ulcer (C4b) and incompetent superficial veins that have reflux directed to the affected skin area, we suggest surgery or an alternative ablation technique of the incompetent superficial veins in addition to standard compressive therapy to prevent ulceration. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: See comments to guidelines 6.1-6.3.

Regarding combined superficial and perforator venous reflux with or without deep venous reflux and active venous leg ulcer, guideline 6.5 reports:

*“In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins in addition to standard compressive therapy to aid in ulcer healing and to prevent recurrence. [GRADE 2; LEVEL OF EVIDENCE C]”.*

WE PROPOSE TO CHANGE GUIDELINE 6.5 TO:

*In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux*

*directed to the ulcer area, in addition to pathologic perforating veins (outward flow of >500 ms duration) located beneath or associated with the ulcer bed, we suggest treatment of the incompetent superficial veins in addition to standard compressive therapy to aid in ulcer healing and to prevent recurrence. [GRADE 2; LEVEL OF EVIDENCE B]*

*Treatment of the incompetent perforating veins can be performed simultaneously with correction of reflux in saphenous trunks or can be staged with re-evaluation of perforating veins for persistent incompetence after correction of truncal reflux. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: Perforating vein treatment is controversial due to contrasting evidence from literature data, especially in PTS and secondary superficial and perforating vein reflux. The role of perforating vein ablation alone or concomitant with treatment of refluxing saphenous trunks awaits results of properly conducted RCTs. The diameter of a perforating vein has limited value.<sup>44, 45, 51-56</sup>

Regarding combined superficial and perforator venous reflux with or without deep venous disease and skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5), guideline 6.6 reports:

*“In a patient with skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic perforating veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. [GRADE 2; LEVEL OF EVIDENCE C]* Treatment of the incompetent perforating veins can be performed simultaneously with correction of axial reflux or can be staged with re-evaluation of perforator veins for persistent incompetence after correction of axial reflux. *[GRADE 2; LEVEL OF EVIDENCE C]”*

WE PROPOSE TO CHANGE GUIDELINE 6.6 TO:

*In a patient with skin changes at risk for venous leg ulcer (C4b) or healed venous ulcer (C5), and with incompetent superficial veins that have reflux to the ulcer bed, in addition to pathologic per-*

*forating veins (outward flow of >500 ms duration) located beneath or associated with the healed ulcer bed, we suggest surgery or an alternative ablation technique of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer. [GRADE 2; LEVEL OF EVIDENCE B] Treatment of the incompetent perforating veins can be performed simultaneously with correction of reflux in saphenous trunks or can be staged with re-evaluation of perforating veins for persistent incompetence after correction of truncal reflux. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: See comments for guideline 6.5.

Regarding pathologic perforator venous reflux in the absence of superficial venous disease, with or without deep venous reflux, and a healed or active venous ulcer, guideline 6.7 reports:

*“In a patient with isolated pathologic perforator veins (outward flow of >500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed regardless of the status of the deep veins, we suggest ablation of the “pathologic” perforating veins in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE 2; LEVEL OF EVIDENCE C]”.*

WE PROPOSE TO CHANGE GUIDELINE 6.7 TO:

*In a patient with isolated pathologic perforating veins (outward flow of >500 ms duration) located beneath or associated with the healed (C5) or active ulcer (C6) bed we suggest surgery or an alternative ablation technique of the “pathologic” perforating veins in case of failure of standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: As perforator vein surgery is controversial (see references reported above) we suggest limiting their treatment to patients in which other therapeutic procedures have failed.

Regarding treatment alternatives for pathologic perforator veins guideline 6.8 reports:

*“For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound-guided sclerotherapy or endovenous thermal ablation (radiofrequency*

*or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin. [GRADE 1; LEVEL OF EVIDENCE C]”*

WE PROPOSE TO CHANGE GUIDELINE 6.8 TO:

*For those patients who would benefit from pathologic perforator vein ablation, we recommend treatments by percutaneous techniques, which do not need incisions in areas of compromised skin, over open venous perforator surgery. [GRADE 1; LEVEL OF EVIDENCE C]*

Comment: Every technique that avoids incisions through compromised skin, from ultrasound-guided foam sclerotherapy to subfascial endoscopic perforating vein surgery (SEPS), is preferable to open venous perforator surgery.

WE PROPOSE TO INCLUDE A NEW GUIDELINE FOR VENOUS ULCERS COMPLICATED BY ARTERIAL INVOLVEMENT, THE SO-CALLED “MIXED ULCERS” WHICH CONSTITUTE ABOUT 20% OF LEG ULCERS:

Guideline 6.8a: Interventional procedures and compression therapy for venous ulcer with simultaneous arterial disease, “mixed ulcer”

*In patients with mixed ulcers of venous and arterial origin we suggest one of the following four treatment options.*

*1. Modified compression only for patients with less severe arterial disease: ankle brachial pressure index [ABPI] >0.5 or absolute ankle pressure >60 mmHg (see also guideline 5.4).<sup>57-59</sup>*

*2. Interventional treatment of superficial venous incompetence alone associated with compression therapy.<sup>46</sup>*

*3. Arterial intervention as the first method of choice in patients with critical limb ischemia (ABPI <0.5, toe pressure <30 mmHg).<sup>60</sup>*

*4. Combined arterial and superficial venous intervention.<sup>61</sup> [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: The relative severity of the circulatory disturbances will guide the choice of treatment options.

WE AGREE WITH GUIDELINE 6.10 AND PROPOSE TO LEAVE IT UNCHANGED BUT TO INCREASE THE LEVEL OF EVIDENCE. THE CHANGE PROPOSED IS:

*In a patient with infra-inguinal deep venous reflux and skin changes at risk for venous leg ulcer*

(C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recommend against deep vein ligation of the femoral or popliteal veins as a routine treatment. [GRADE 1; LEVEL OF EVIDENCE C]

Comment: Strong recommendation with low level of scientific evidence.<sup>62, 63</sup>

Regarding deep venous reflux with skin changes at risk for venous leg ulcer (C4b), healed (C5) or active (C6) venous leg ulcer - primary valve repair, guideline 6.11 reports:

“In a patient with infrainguinal deep venous reflux and skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we suggest individual valve repair for those who have axial reflux with structurally preserved deep venous valves in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 6.11 TO:

*In a patient with infrainguinal deep venous reflux and symptoms or signs not responding to conservative treatment, we recommend individual internal valve repair for those who have deep axial reflux with structurally preserved deep venous valves in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE 1; LEVEL OF EVIDENCE C]*

Comment: We propose to limit valve repair to the patients not responsive to conservative treatment (compression therapy, lifestyle changes) and to add “internal” to valve repair, as we know that outcomes of internal repair are better than those of external repair. We propose modifying the grade to 1C.<sup>64</sup>

Regarding Proximal chronic total venous occlusion/severe stenosis with skin changes at risk for venous leg ulcer (C4b), healed (C5) or active (C6) venous leg ulcer - Endovascular repair, guideline 6.14 reports:

“In a patient with inferior vena cava or iliac vein chronic total occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, that is associated with skin changes at risk for venous leg ulcer (C4b), healed venous leg ulcer (C5), or active venous leg ulcer (C6), we recom-

mend venous angioplasty and stent recanalization in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE 1; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 6.14 TO:

*In a patient with inferior vena cava and/or iliac vein chronic total occlusion or severe stenosis without common femoral vein occlusion, with or without lower extremity deep venous reflux disease, that is associated with symptoms or signs not responding to conservative treatment, we recommend venous angioplasty and stent recanalization in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence. [GRADE 1; LEVEL OF EVIDENCE C]*

Comment: See also comment to guideline 6.11; femoral vein occlusion requires an additional endophlebectomy.<sup>65</sup>

WE AGREE WITH GUIDELINE 6.15 BUT PROPOSE A MINOR LINGUISTIC CHANGE FROM “TREATMENT” TO “TREATMENTS”:

*In a patient with inferior vena cava and/or iliac vein chronic occlusion or severe stenosis, with or without lower extremity deep venous reflux disease, which is associated with a recalcitrant venous leg ulcer and who have failed endovascular treatments, we suggest open surgical bypass using an externally supported ePTFE graft in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: One or more additional endovenous interventions may be required, after failure of a first attempt of recanalization.

### Ancillary measures

Regarding systemic drug therapy, guideline 7.2 reports:

“For long-standing or large venous leg ulcer, we recommend treatment with either pentoxifylline or micronized purified flavonoid fraction used in combination with compression therapy. [GRADE 1; LEVEL OF EVIDENCE B]”.

WE PROPOSE TO CHANGE GUIDELINE 7.2 TO:

*For long-standing or large venous leg ulcer, we recommend treatment with either pentoxifylline, mi-*

*cronized purified flavonoid fraction (MPFF) or sulodexide, all used in combination with compression therapy. [GRADE 1; LEVEL OF EVIDENCE B]*

Comment: Other than the well-established and described effects for both pentoxifylline and MPFF, recent evidence strongly supports the data described in the randomized multicenter placebo-controlled trial using the profibrinolytic and antithrombotic drug, sulodexide (purified glycosaminoglycan), showing improved VLU healing in 235 patients treated for 3 months (ref. 461 of SVS-AVF guidelines). In fact, both clinical and experimental evidences (both *in vitro* and *in vivo*) demonstrate that sulodexide can improve healing through specific inhibition of proteolytic processes and inflammatory pathways, suggesting its use for a successful therapeutic approach combined with compression.<sup>66-71</sup>

Regarding manual lymphatic drainage, guideline 7.4 reports:

“We suggest against adjunctive lymphatic drainage for healing of the chronic venous leg ulcers. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE GUIDELINE 7.4 TO:

*We suggest adjunctive physical therapy and manual lymphatic drainage when the ulcer is associated with reduced ankle range of motion (aROM) due to chronic edema and skin fibrosis, to improve the aROM. [GRADE 2; LEVEL OF EVIDENCE B]*

Comment: It was demonstrated that manual lymphatic drainage improves aROM in legs with skin fibrosis. Improvement of ankle flexibility is one of the goals of the rehabilitative programs recommended by guideline 7.3.<sup>59-62</sup>

Regarding balneotherapy, guideline 7.5 reports:

“We suggest balneotherapy to improve skin trophic changes and quality of life in patients with advanced venous disease. [GRADE 2; LEVEL OF EVIDENCE B]”.

WE PROPOSE TO CHANGE GUIDELINE 7.5 TO:

*We suggest against balneotherapy to improve skin trophic changes. Saltem per aquam (SPA) therapies may improve quality of life and adherence to physical treatments in patients with ad-*

*vanced venous disease. [GRADE 2; LEVEL OF EVIDENCE C]*

Comment: No study has demonstrated that balneotherapy improves skin changes. No study has demonstrated that balneotherapy reduces the incidence of VLUs. No study has evaluated the effects of SPA therapies in ulcerated patients.

## Primary prevention

Regarding Primary prevention - Clinical CEAP C3-4 primary venous disease, guideline 8.1 reports:

“In patients with clinical CEAP C3-4 disease due to primary valvular reflux, we recommend compression, 20 to 30 mmHg, knee or thigh high. [GRADE 2; LEVEL OF EVIDENCE C]”.

WE PROPOSE TO CHANGE RECOMMENDATION GRADING TO BEST PRACTICE. GUIDELINE 8.1 SHOULD BE CHANGED TO:

*In patients with clinical CEAP C3-C4 disease due to primary valvular reflux, we suggest 20-30 mmHg compression, knee or thigh high. [BEST PRACTICE]*

Comment: We do not have any data reporting elastic stockings' effectiveness in preventing VLU formation. If we followed the recommendation rules used in the entire document, we should recommend “against” elastic compression stockings to prevent VLU in the absence of data. Nevertheless recommending against compression in CVI seems to be too strong. As most doctors recommend elastic stockings in the advanced stages of CVI, BEST PRACTICE seems to be more appropriate.

Regarding Primary prevention - Clinical CEAP C1-4 post-thrombotic venous disease, guideline 8.2 reports:

“In patients with clinical CEAP C1-4 disease related to prior deep venous thrombosis (DVT), we recommend compression, 30 to 40 mmHg, knee or thigh high. [GRADE 1; LEVEL OF EVIDENCE B]”.

WE PROPOSE TO CHANGE GUIDELINE 8.2 TO:

*In patients with clinical CEAP C1-C4 disease related to prior DVT, we recommend compression of at least 20-30 mmHg pressure, and 30-40 mmHg whenever possible, knee or thigh high. [GRADE 1; LEVEL OF EVIDENCE B]*

Comment: Compression pressure of 30-40 mmHg cannot be considered mandatory.

Prandoni used 30-40 mmHg but reports: "To our knowledge, there are no studies that have compared different compression strengths of stockings to prevent PTS. It would be worth studying the effectiveness of lighter compression (20-30 mmHg) stockings as they are easier to apply, especially for elderly patients, than 30-40 mmHg stockings".<sup>76</sup>

Aschwanden used stockings with a compression pressure of 26-36 mmHg.<sup>77</sup>

Blattler and Partsch 23-33 mmHg<sup>78</sup> just as Arpaia<sup>79</sup> assessing the recanalization rate after a DVT.

Regarding Primary prevention - Education measures, guideline 8.4 reports:

"In patients with C1-4 disease, we suggest patient and family education, regular exercise, leg elevation when at rest, careful skin care, weight control, and appropriately fitting foot wear. [BEST PRACTICE]"

WE PROPOSE TO CHANGE GUIDELINE 8.4 TO:

*In patients with C3-C6 disease, we suggest patient and family education, regular exercise, leg elevation when at rest, careful skin care, weight control and appropriately fitting foot wear. [BEST PRACTICE] Social and psychological supports are recommended in patients with severe venous disease in which depression or anxiety impede adherence to programs of primary prevention, physical activity and self-management. [BEST PRACTICE]*

Comment: Guidelines regard VLU; we suggest that these measures be applied in patients at risk of VLU or in patients who do have VLU.

Approximately a third of patients with C5-C6 disease score "at-risk" of depression (scores of 5 or above on the Geriatric Depression Scale (GDS). It is well known that depression, stress and anxiety are associated with delayed wound healing.<sup>80</sup> Moreover, the presence of leg ulcers has been significantly associated with being single with poorer levels of social support, as demonstrated by measurements of Medical Outcomes Study (MOS) Social Support Scale. The strong and statistically significant relationship between social support and recurrence is sup-

ported by the finding of higher measures of social interaction in patients whose ulcers did not recur.<sup>81</sup>

In conclusion, social support influences the level of physical activity and self-management, thus preventing worsening of CVI and ulcer recurrence.<sup>82, 83</sup>

## Conclusions

In summary, the UIP Committee on VLU completely agreed with 43 out of 75 SVS-AVF guidelines, which were not reported in this document, and substantially agreed just rephrasing or proposing slight semantic changes for 19 of them.

Some discrepancies were reported concerning the content of the remaining guidelines.

A change in grading or level of recommendation was proposed in six and recommendations were reversed in three guidelines. In addition, it was proposed to summarize four recommendations concerning surgical reconstruction of VLUs in just one and to add three new recommendations respectively on autolytic debridement, compression therapy and surgical interventions of venous ulcers when arterial impairment coexists.

It should be underlined that the SVS-AVF guidelines on VLUs still propose "best practice" in ten guidelines, and grade 2 with evidence C in 35 guidelines. It should be acknowledged that, in the field of VLUs, 60% of guidelines do not contain recommendations but only suggestions, with very weak evidence (and this ratio remains about the same after our proposals for changes); hence there is a need for more scientific research in this important field, in order to produce recommendations rather than suggestions, and to strengthen the level of evidence where it is still weak.

The UIP Committee on VLUs greatly appreciates the enormous and excellent work performed by the American colleagues and confirms endorsement of a major part of the present SVS-AVF guidelines.

Some suggestions and comments, summarized in this document, may not only be useful in future revisions – preferably to be realised in a joint effort with SVS, AVF, UIP and potentially other scientific societies –, but may also contrib-

ute to future research in the field of VLU. All these efforts should aim at improving care for patients with VLU, eventually reducing the prevalence of this debilitating disease and associated healthcare burden.

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

Received on February 16, 2015; accepted for publication on April 16, 2015.

Epub ahead of print on April 21, 2015.