

## **GLOBAL GUIDELINES TRENDS & CONTROVERSIES**

### **in lower limb venous and lymphatic disease**

*Narrative literature revision & experts opinions*

*following the vWINter international meeting in Phlebology, Lymphology & Aesthetics,*

*Jan 23-25, 2019*

#### *Authors & Affiliations*

Gianesini S,<sup>1</sup> Obi A,<sup>2</sup> Onida S,<sup>3</sup> Baccellieri D,<sup>4</sup> Bissacco D,<sup>5</sup> Borsuk D,<sup>6</sup> Campisi C,<sup>7</sup> Campisi CC,<sup>8</sup> Cavezzi A,<sup>9</sup> Chi YW,<sup>10</sup> Chunga J,<sup>11</sup> Corda D,<sup>12</sup> Crippa A,<sup>13</sup> Davies AH,<sup>3</sup> De Maeseneer M,<sup>14</sup> Diaz J,<sup>15</sup> Ferreira J,<sup>16</sup> Gasparis A,<sup>17</sup> Intriago E,<sup>18</sup> Jawien A,<sup>19</sup> Jindal R,<sup>20</sup> Kabnick L,<sup>21</sup> Latorre A,<sup>22</sup> Lee BB,<sup>23</sup> Liew NC,<sup>24</sup> Lurie F,<sup>25</sup> Meissner M,<sup>26</sup> Menegatti E,<sup>1</sup> Molteni M,<sup>27</sup> Morrison N,<sup>28</sup> Mosti G,<sup>29</sup> Narayanan S,<sup>30</sup> Pannier F,<sup>31</sup> Parsi K,<sup>32</sup> Partsch H,<sup>33</sup> Rabe E,<sup>34</sup> Raffetto JD,<sup>35</sup> Raymond-Martimbeau P,<sup>36</sup> Rockson S,<sup>37</sup> Rosukhovski D,<sup>38</sup> Santiago F,<sup>39</sup> Schul A,<sup>26</sup> Schul M,<sup>40</sup> Shaydakov E,<sup>38</sup> Sibilla MG,<sup>1</sup> Tessari L,<sup>41</sup> Tomaselli F,<sup>42</sup> Urbanek T,<sup>43</sup> van Rijn M,<sup>14</sup> Wakefield T,<sup>2</sup> Wittens C,<sup>44,45</sup> Zamboni P,<sup>1</sup> Bottini O.<sup>46</sup>

1. University of Ferrara, Ferrara (ITALY)

2. University of Michigan, Ann Arbor (USA)

3. Imperial College London, London (UK)

4. San Raffaele Scientific Institute, Milan (ITALY)

5. University of Milan, Milan (ITALY)

6. Clinic of Phlebology and Laser Surgery, “Vasculab” Ltd., Chelyabinsk (RUSSIA)

7. University of Genoa, Genoa (ITALY)

8. University of Catania, Catania (ITALY)

9. Eurocenter Venalinfa, Ascoli Piceno (ITALY)

10. University of California Davis, San Francisco (USA)

11. Glomach Medic, Lima (PERÙ)
12. Corda Clinic, Pavia (ITALY)
13. Crippa Clinic, Milan (ITALY)
14. Erasmus Medical Center, Rotterdam (NETHERLANDS)
15. Vanderbilt University Medical Center, Nashville (USA)
16. Instituto Brasileiro de Flebologia, Sao Paulo (BRAZIL)
17. Stony Brook University, New York (USA)
18. Espiritu Santo University, Guayaquil, (ECUADOR)
19. Collegium Medicum, University of Nicolaus Copernicus, Bydgoszcz, (POLAND)
20. Punjab University, Chandigarh (INDIA)
21. Kabnick Vein Center, Morristown (USA)
22. Universidad Autonoma de Bucaramanga, Bucaramanga (COLOMBIA)
23. George Washington University, Washington (USA)
24. Putra University, Serdang (MALAYSIA)
25. Jobst Vascular Institute, Toledo (USA)
26. University of Washington, Seattle (USA)
27. UOC Cure Subacute, IRCCS Maugeri Milano, (ITALY)
28. Center for Vein Restoration, Mesa, Arizona (USA)
29. Barbantini Clinic, Lucca (ITALY)
30. The Harley Street Heart & Vascular Center (SINGAPORE)
31. University of Cologne, Cologne (GERMANY)
32. New South Wales University, Sidney (AUSTRALIA)
33. University of Wien, Wien (AUSTRIA)
34. University of Bonn, Bonn (GERMANY)
35. Harvard University, Boston (USA)
36. Dallas Noninvasive Vascular Laboratory (USA)

37. Stanford University School of Medicine, Stanford California (USA)
38. Institute of Experimental Medicine, Moscow (RUSSIA)
39. Venous & Lymphatics Disease Institute, Goiás (BRAZIL)
40. Indiana University, Lafayette Indiana (USA)
41. Bassi-Tessari foundation, Peschiera del Garda (ITALY)
42. University Consortium Humanitas Roma (ITALY)
43. Medical University of Silesia, Krakow (POLAND)
44. Maastricht University Medical Center, Maastricht (NETHERLANDS)
45. Uniklinik Aachen, Aachen (GERMANY)
46. Universidad de Buenos Aires, Buenos Aires (ARGENTINA)

**CORRESPONDING AUTHOR:**

Sergio Giancesini, MD PhD FACS

University of Ferrara (ITALY)

Via Aldo Moro 8, 44123 Ferrara, ITALY

Mail: sergiogiancesini@gmail.com Tel: 0039 3498012304

ORCID ID 0000-0002-0440-5975

**Running Head:** *Global guidelines similarities and controversies*

**Keywords:** Phlebology, Lymphology, Guidelines, Recommendation, Evidence, GRADE.

## ABSTRACT

Guidelines are fundamental in addressing everyday clinical indications and in reporting the current evidence-based data of related scientific investigations. At the same time, a spatial and temporal issue can limit their value. Indeed, variability in the recommendations can be found both among the same nation different scientific societies and among different nations/continents. On the other side, Garcia already published in 2014 data showing how, after 3 years in average, one out of 5 recommendations gets outdated (*Martinez Garcia LM, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. CMAJ 2014;186(16):1211–1219*). The present document reports a narrative literature revision on the major international recommendations in lower limb venous and lymphatic disease management, focusing on the different countries guidelines trends and controversies from all the continents, while identifying new evidence-based data potentially influencing future guidelines. World renowned experts opinions are also provided. The document has been written following the recorded round tables scientific discussions held at the v-WINter international meeting (January 22-26, 2019; Cortina d'Ampezzo, Italy) and the pre and post-meeting literature search performed by the leading experts.

## **SCIENTIFIC PROJECT RATIONALE AND AIM**

Guidelines are fundamental in addressing everyday clinical indications and in reporting the current evidence-based data of related scientific investigations. At the same time, a spatial and temporal issue can limit their value. Indeed, variability in the recommendations can be found both among the same nation different scientific societies and among different nations/continents. On the other side, Garcia already published in 2014 data showing how, after 3 years in average, one out of 5 recommendations get outdated (*Martinez Garcia LM, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. CMAJ 2014;186(16):1211–1219*).

Aim of the present document is to report a narrative literature revision on the major international recommendations in lower limb venous and lymphatic disease management, focusing on the different countries guidelines trends and controversies, while identifying new evidence-based data potentially influencing future guidelines. World renowned experts opinions are also provided.

The document includes also the 5 best blind peer-reviewed free abstracts among the 64 submitted to the vWINter meeting. The abstracts have been selected by an international scientific committee of top experts who were blinded in the revision process and who scored the best five works after the authors related talk at the meeting.

## **METHODOLOGY**

An international meeting dedicated to venous and lymphatics guidelines was held in Cortina d'Ampezzo (ITALY) on January 23-25, 2019. World renowned experts came from 41 countries of all the continents. Along the previous months, working groups were created on different topics. Every working group was composed by one under 40 years old involved in the phlebo-lymphology field and by 5 top experts of a specific topic. The under 40 prepared the sum up of the current international recommendations, guided by the 5 leading experts. The sum up was than presented at the meeting and extensively discussed among the experts first, involving the audience for further input in the final part of the dedicated

sections. All the discussion was recorded. In the three months after the meeting the present document was drafted.

The document is divided in 11 sections, one per topic. Every section is divided in three chapters:

1. international current recommendations
2. significant new evidence-based data potentially influencing future recommendations
3. sum up of the expert opinions, as discussed during the meeting and than expanded by the literature search after the same meeting.

The material included in the document is in the form of a narrative revision of the literature performed by the experts and no systematic approach has been used. The intent of the present document is to transversally analyse the eventual heterogeneity in current international guidelines, assess the need of update the recommendations and to pave the way for further systematic revisions of global guidelines and related new evidence-based data. In any way the herein reported analysis is intended to alter the value of current guidelines, which represent the result of a systematic revision of the literature. At the same time, the related considerations are not presented as a substitute for the advice of a physician or other knowledgeable health care professional or provider.

## **LITERATURE SEARCH AND SELECTION**

The under 40 vein and lymphatic specialists, together with and under the supervision of the world renowned experts involved in the different sections and reported in the authorship list, performed the literature search in PubMed, Embase, Cinhal, and the Cochrane library up to March 31, 2019. National experts from all the continents involved as “masters” of the different sections of the vWINter meeting and of this document were asked to identify the guidelines to be considered of reference for their geographical regions.

The under 40 experts of the different 11 sections drafted a first manuscript following the discussion among the expert opinions held during the vWINter meeting. The international experts of all the sections reviewed and implemented the draft adding pertinent literature and opinions.

Criteria for search and selection of the quoted references were:

- English Language
- Indexed journals publications
- No restrictions on the number of subjects enrolled in the study.

In case of data coming from not indexed and/or from not English written journals, they were included only if considered of paramount value for the specific topic analysis.

The chapters dedicated to the significant new evidence-based data that were included in all the 11 different sections focused on the last 5 years publications.

## **FINDINGS**

Despite the globally available and shared evidence-based scientific literature, heterogeneity can be found whenever comparing different guidelines of different countries and sometimes even of different institutions of the same nation. Recommendations for lower limb venous and lymphatic disease management should be updated more often and in a cooperative global way among different continents and related scientific societies. To the best of our knowledge, this document represents the only available attempt to assess homogeneity and actualization of the current guidelines in phlebology. The results of this international analysis could pave the way for a synergistic multi-specialty and inter-society systematic and homogeneous update of the future evidence-based recommendations.

### **SECTIONS (authors in brackets)**

#### **1. Lower limb venous ultrasound**

*(Schul A, De Maeseneer M, Jawien A, Lurie F, Shaydakov E, Urbanek T, Gianesini S)*

#### **2. Endovenous saphenous ablation**

*(Borsuk D, Davies A, Kabnick L, Shaydakov E, Urbanek T, Wakefield T, Gianesini S)*

#### **3. Bandaging, Adjustable Compression Wraps, Intermittent Pneumatic Compression**

*(Intriago E, Chi YW, Lurie F, Mosti G, Partsch H, Wittens C, Giancesini S)*

#### **4. Graduated Elastic Stockings**

*(Menegatti E, Chi YW, Lurie F, Mosti G, Partsch H, Wittens C, Giancesini S)*

#### **5. Sclerotherapy for varicose veins**

*(Chunga J, Cavezzi A, Morrison N, Parsi K, Raymond-Martimbeau P, Tessari L, Giancesini S)*

#### **6. Aesthetic phlebology**

*(Rosukhovski D, Crippa A, Ferreira J, Santiago F, Schul M, Tomaselli F, Giancesini S)*

#### **7. Acute and chronic deep venous disease**

*(Baccellieri D, van Rijn M,\* Gasparis T, Jindal R, Meissner M, Wittens C, Zamboni P, Giancesini S)*

\*the author equally contributed as the first author of the section

#### **8. Venous Active Drugs**

*(Bissacco D, Mosti G, Narayanan S, Rabe E, Raffetto JD, Simkin R, Giancesini S)*

#### **9. Ulcer management**

*(Sibilla MG, Mosti G, Narayanan S, Rabe E, Raffetto JD, Simkin R, Giancesini S)*

#### **10. Lower limb lymphedema**

*(Onida S, Campisi C, Campisi CC, Corda D, Latorre A, Lee BB, Rockson S, Giancesini S)*

#### **11. Venous thrombosis management**

*(Obi A, Diaz D, Liew NC, Molteni M, Pannier F, Raffetto J, Wakefield T, Giancesini S)*

#### **12. SCIENTIFIC WORK LIMITATIONS**

#### **13. REFERENCES**

#### **CONFLICTS OF INTEREST**

All the authors declared NO conflicts of interest with the exception of the following:

- Liew NC: Chairperson of Asian Venous Thrombosis Forum- Forum sponsored by educational grant from Covidien Singapore, and Cardinal Health



- Molteni M: Consultant and lecturer for Bayer, BMS, Boeringher-Ingelheim, Daiichi-Sankyo, Guidotti-Malesci, Novartis, Pfizer, Portola, Sanofi, Techdow
- Morrison N: research grant, speakers bureau/consultant (MEDTRONIC)/Educational grant, speakers bureau (MEDI)/speakers bureau (MERZ/ANGIODYNAMICS)/Speaker bureau (BTG)
- Wakefield T: unpaid consultant to Selexys Corporation

### **ACKNOWLEDGMENTS**

We thank the following colleagues for their valuable insights during the v-WINter international meeting open discussions:

Agus G, Albernaz L, Annoni F, Cappelli M, Cavallini A, Dragic P, Diaz J, Ebner J, El-Chamali S, El-shamali S, Gogia A, Grill M, Hussein E, Jia N, Khilnani N, Lattimer C, Lawrence P, Marek S, Maurins U, Memprim F, Obermayer A, Oberto S, Padaria S, Palmiste V, Pittman C, Ragg JC, Ricci E, Sasaki Y, Scuderi A, Taha W, Ugliola M, Visconti G, Weingartner J, Whiteley M, Yamaki T, Tessari M, Zini F, Zolotukhin I.

## **1. LOWER LIMB VENOUS ULTRASOUND**

### **MAIN TOPICS**

- Venous hemodynamics & ultrasound setting
- Venous thrombosis
- Ilio-femoral stenosis
- Pelvic venous assessment
- Post-op ultrasound follow-up

### **ANALYSED GUIDELINES**

- **GLOBAL 2011:** International Union of Phlebology (UIP). Duplex Ultrasound Investigation of the Veins of the Lower Limbs after Treatment for Varicose Veins.<sup>1</sup>
- **USA 2011:** Society for Vascular Surgery (SVS) and the American Venous Forum (AVF).<sup>2</sup>
- **USA 2012:** AVF Multicenter assessment of venous reflux by duplex ultrasound.<sup>3</sup>
- **USA 2014:** American Vein & Lymphatic Society (AVLS)(former American College of Phlebology, ACP) guidelines.<sup>4</sup>
- **SPAIN 2015:** Capitulo Espanolo de Flebologia Y Linfologia - Guías de Práctica Clínica en Enfermedad Venosa Crónica.<sup>5</sup>
- **EUROPE 2015:** European Society for Vascular Surgery guidelines (ESVS).<sup>6</sup>
- **USA 2015:** American Institute of Ultrasound in Medicine (AIUM) Practice Guidelines for the Performance of Peripheral Venous Ultrasound Examinations.<sup>7</sup>
- **LAT-AM 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>
- **KOREA 2017:** Ultrasonography of the lower extremity veins: anatomy and basic approach.<sup>9</sup>
- **SWITZERLAND 2017:** Clinical and duplex ultrasound evaluation of lower extremities varicose veins – a practical guideline.<sup>10</sup>

- **GLOBAL 2018:** Management of chronic venous disorders of the lower limb. Guidelines according to scientific evidence. European Venous Forum (EVF), International Union of Angiology (IUA), Cardiovascular Disease Educational and Research Trust (UK), International Union of Phlebology (UIP).<sup>11</sup>
- **USA 2018:** International Accreditation Center (IAC) Standards and Guidelines for Vascular Testing Accreditation.<sup>12</sup>

## **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

### **1. Venous hemodynamics & ultrasound setting**

Among the analysed guidelines and consensus documents, there is a general agreement on performing the reflux screening in standing, using the transverse view for patency and diameter measurement and the longitudinal scanning for proper spectral analysis.<sup>1-12</sup>

Yet, only sparse recommendations were found in favour of a standardized ultrasound parameters setting. The sample volume opening is left to the operator discretion and only the AVF 2012<sup>3</sup> and Swiss 2017<sup>10</sup> practical guidelines specify a steering of < 60%.

Flow augmentation is generally reported in the guidelines by means of Valsalva manoeuvre for proximal lower extremity and pelvic vein evaluation. Calf squeeze is usually suggested for distal vein assessment. Concerns with the standardization favour the use of pneumatic cuffs rather than manual squeezing. Yet, only the Swiss document<sup>10</sup> includes also the active dorsi-flexion manoeuvre.

While there is general agreement in recommending the evaluation of all the systems segments whenever looking for reflux, not all the guidelines include at which level the caliber measurement should be assessed (Tab 1.1)

	GLOBAL UIP 2011	USA AVF/SVS 2011	USA AVF 2012	USA AVLS 2014	USA AIUM 2015	EUROPE ESVS 2015	LATAM 2016	Switzerland 2017	Korea 2017
LOCATION	- 3 cm below  - SFJ - mid thigh - knee - mid-calf	Not Reported	Not Reported	At the mid thigh and at the knee is desirable	Not Reported	- 3 cm below SFJ  GSV - mid thigh - knee - lower leg  AASV - Mid-thigh  SSV  SPJ	Not Reported	- 3 cm below SFJ - mid-thigh - knee - mid-calf	Not Reported

**Tab. 1.1: Saphenous diameter assessment points location according to international guidelines.**

While there is general agreement in recommending the evaluation of all the systems segments whenever looking for reflux, not all the guidelines include at which level the caliber measurement should be assessed. Sapheno-femoral junction (SFJ); Great Saphenous Vein (GSV); Anterior Accessory Saphenous Vein (AASV); Small Saphenous vein (SSV); Sapheno-Popliteal Junction (SPJ).

## 2. Thrombosis assessment

Limited (2-points) or complete compression ultrasound have been recommended for the diagnosis of deep vein thrombosis (DVT) in several guidelines. In the evaluated consensus documents, protocols for deep venous thrombosis scanning are widely variable (tab 1.2).

Only the AVF/SVS 2011,<sup>2</sup> AIUM 2015<sup>7</sup> and Korea 2017<sup>9</sup> documents mention the distance between compression points along the vein to be used for thrombosis assessment, varying from 2 to 5 cm in the different indications.

GLOBAL UIP 2011	USA AVF/SVS 2011	USA AVLS 2014	USA AIUM 2015	LATAM 2016	SWITZERLAND 2017	KOREA 2017	USA IAC 2018
All segments	All segments	Not reported	- Common femoral - Popliteal - Symptomatic areas	Not reported	- Deep femoral - Femoral - Popliteal - Calf is recommended in specific clinical cases (e. g. prior deep vein thrombosis, venous ulcer)	All segments	- Common femoral - Sapheno-femoral junction - Femoral vein - Popliteal vein - Posterior tibial veins - Peroneal veins; - Additional images to document areas of suspected thrombus

**Tab. 1.2: Anatomical location where international guidelines recommend compression ultrasound for venous thrombosis assessment.**

Only the AVF/SVS 2011,<sup>2</sup> AIUM 2015<sup>7</sup> and Korea 2017<sup>9</sup> documents mention the distance between compression points along the vein to be used for thrombosis assessment, varying from 2 to 5 cm in the different indications.

In 2018 the Society of Radiologists in Ultrasound published a consensus document pointing out the need of a standardized lower extremity DVT scanning protocol. In particular, the document recommended a comprehensive scanning (compression ultrasound, pulsed wave and colour Doppler) from thigh to ankle, with focus on specific sites, rather than a limited or even complete ‘compression only’ examination. The panel recommended to include at least two sites of colour and spectral analysis in the leg, not relying just on compression ultrasound.<sup>13</sup>

Whether or not to include comprehensive duplex scanning of the calf veins is still a subject of debate. It points at the need for homogeneous protocols, not only for diagnosis, but also for treatment of DVT isolated to the calf. The indication for treating calf vein DVT is reported heterogeneously in the different guidelines.<sup>14-17</sup> This has been analysed in the section of the present document dedicated to the anticoagulation session.

Noteworthy, the panel recommended against ultrasound scanning in case of a negative appropriately sensitive D-dimer test with an unlikely pretest probability. The panel also emphasized the utility of performing another scan at the end or just after the anticoagulation period in order to establish a new baseline. On the other hand, repeated scans are not recommended during the treatment, unless symptomatic changes are reported.<sup>13</sup>

The panel also recommended to avoid the term “chronic DVT” in order to avoid potential overtreatment with prolonged anticoagulation. Instead, the term “chronic post-thrombotic change” should be used to describe fibrotic scars, trabeculae and wall thickening in deep veins after previous DVT.<sup>13</sup>

Special attention should be paid to the assessment and management of superficial venous thrombosis. The International Union of Angiology/UIP/Central European Venous Forum 2012 Consensus

Document<sup>18</sup> recommended an extensive scan of both the superficial and deep venous system in case of clinical suspect. Considering that a concomitant contra-lateral superficial venous thrombosis has been reported up to 25 % of cases,<sup>19</sup> the same consensus recommended the scanning of both limbs.<sup>18</sup>

### **3. Ilio-femoral stenosis**

Limited information is reported in international guidelines regarding standard assessment of the iliac and ilio-caval venous segments, with indications coming mainly from sparse research studies. The main ultrasound features of ilio-femoral stenosis were recently systematized in a paper by Sloves as follows:

1. Reduced vein diameters (common iliac vein<8mm; external iliac vein<7mm; common femoral vein<6mm)
2. Bilateral asymmetric flow patterns within the common femoral and iliac veins
3. Peak vein velocity ratio>2.5
4. External iliac vein reflux
5. Reversal of flow within the internal iliac vein may be indicative of ipsilateral common iliac vein obstruction.<sup>20</sup>

Only AVF/SVS 2011<sup>2</sup> pointed at the possible use of IVUS with a grade 1B recommendation in patients with varicose veins and more advanced chronic venous disease to identify ilio-caval and ilio-femoral pathology.

### **4. Pelvic venous plexus**

In international guidelines, indications are missing also regarding the pelvic system assessment. In 2017, Labropoulos published a dedicated protocol for assessment of inferior vena cava, left renal vein, iliac veins, ovarian veins, trans- and peri-uterine veins, and the tributaries of the internal iliac veins. The connection among pelvic floor and lower extremities are also scanned, focusing on the pelvic escape points. Valsalva and manual distal compression near the iliac fossa are used to elicit the flow, sometimes adding thigh compression.<sup>21</sup>

## 5. Superficial venous disease post-operative ultrasound follow up

Just two of the analysed documents report a timeline for post-op ultrasound assessment following superficial venous treatment (UIP 2011<sup>1</sup> and LATAM guidelines<sup>2</sup>), with evident differences in the recommendations (Tab 1.3).

	GLOBAL UIP 2011	USA AVF7SVS 2011	USA AVLS 2014	USA AIUM 2015	EUROPE ESVS 2015	LATAM 2016
POST-OP TERM	1-4 weeks technical success, thrombosis.. CHIVA second step	Sonographic scan at 24-72 hours to exclude endovenous heat induced thrombosis (EHIT). No other indications are reported.	Not found	Not found	Not found	1 month Residual pathology
SHORT TERM	1 year					6 months Comparison with the 1 M
MEDIUM TERM	2-3 years Too short for long term outcomes, but useful for early changes					12 months Progression, new perforators, complication evolution
LONG TERM	5 years long enough for clinical recurrence					18 months Disease evolution
ALONG TIME	10 years If possible.					24 months If needed

**Tab. 1.3: Timeline for post-operative ultrasound assessment according to international guidelines.**

Just two of the analysed documents report a timeline for post-op ultrasound assessment following superficial venous treatment (UIP 2011<sup>1</sup> and LATAM guidelines<sup>2</sup>), with evident differences in the recommendations.

## SIGNIFICANT RECENT DATA RELATED TO THE MEETING DISCUSSION

### 1. General venous hemodynamics

In 2011, the UIP<sup>1</sup> document recommended the outer vessel wall was considered a reference point for diameter measurement, while in 2018 the DIAGRAVES study by the French Society opted for using the inner diameter.<sup>22</sup>

Active dorsiflexion flow augmentation can produce significant different flow velocities compared to calf squeezing: a fact to be taken into consideration for homogenous data reporting.<sup>23</sup> Steering of the sample volume and cursor alignment becomes particularly challenging for assessing tortuous perforating veins. In 2018, the current definition of perforator incompetence, based on an outward diastolic flow lasting more than 500 msec, was challenged by the introduction of a new Quality Doppler Profile software for perforating vein evaluation. This multi-gate scanning reported a sensitivity of the perforating vein incompetence of just 13.9%, with a specificity of 96.4%.<sup>24</sup>

In the same year, Bechsgaard et al. published data supporting the use of another angle independent spectral analysis (vector flow imaging method) and reported an equally precise but far more accurate flow assessment than with routine duplex ultrasound investigation of perforating veins.<sup>25</sup>

### **3. Ilio-femoral stenosis**

In 2016 one publication pointed out that the absence of flow phasicity is observed in 62.5% of patients with obstructions >80%. This means it cannot be considered the main parameter to report venous stenosis. The author proposed the velocity ratio >2.5 as the most accurate to detect >50% stenosis.<sup>26</sup>

In 2018, Sloves et al pointed out that the definition of iliac stenosis in case of 50% caliber reduction or more, still used by many assessors, is to be abandoned because it is improperly derived from the arterial world.<sup>20</sup> The venous pressure gradient (between proximal and distal segments) is not a good criterium either, as the pressure starts to increase already at 13% caliber reduction: another finding limiting the utility of this parameter in stenosis definition.<sup>27</sup> Recently, Razavi et al<sup>28</sup> demonstrated the appropriateness and better performance of IVUS compared to venography for proper evaluation of the lesion in planning potential stenting. In a similar way, Rossi et al<sup>29</sup> demonstrated the utility of using IVUS as a guidance for stenting.



## **DISCUSSION**

Proper ultrasound setting is fundamental in order to report accurate values and to perform a homogeneous comparison in scientific investigations. A paucity of information is reported in the literature regarding in particular the setting of the sample volume opening, steering and cursor orientation. Future investigations should always report a homogeneous assessment methodology for proper data comparison. A standardization of reporting the augmentation manoeuvre, patient position, and time of the day should be mentioned as all these parameters may influence the ultrasound assessment.<sup>3</sup> In 2006, the concept of proper beam alignment was stressed by the Society for Vascular Medicine and Biology guidelines, showing an underestimation of the assessed velocity whenever not positioning the cursor parallel to the vessel axis.<sup>30</sup> Apart from steering, clear indications about where positioning the sample volume along the depth of a perforating vein are generally missing in the guidelines. Future guidelines should look for reporting a globally agreed scanning protocol, to guarantee the most accurate assessment and homogeneous reporting, additionally including the post-op follow-up timing. Last but not least, a clear standardization of the sonographic training, both for physicians and vascular technologists, in addition to the introduction of standardized reporting methods are mandatory. As mentioned above, a post/prestenotic velocity ratio  $>2.5$  has been proposed as one of the criteria for significant iliac vein stenosis,<sup>29</sup> yet such velocity ratio has not been validated as outcome measures in clinical trials and collateral circulation could keep the velocity ratio normal despite a significant obstruction. Raju introduced the concept of optimal outflow caliber by proposing specific values for diameter and area,<sup>27,31</sup> but also these criteria have not been validated and their correlation with pressure values and clinical outcome is not clear yet. Interestingly, the use of IVUS was graded 1B in 2011 AVF/SVS guidelines<sup>2</sup> and was downgraded to 2C in the 2014 recommendations by the same group.<sup>32</sup> Validated tests for quantification of obstruction are still missing. Moreover, body position (lying vs semi-recumbent position) could significantly alter the outcome of obstruction assessment. This certainly needs further investigation. A globally accepted, standardized protocol for DVT scanning is still missing. When looking within a single country, significant differences in related protocols are

identified. The timing of the ultrasound follow up after superficial venous thrombosis is also to be defined according to proper evidence and future investigations on this topic are encouraged. Proper terminology should be used in a uniform way in all the countries, particularly avoiding confusing terms. A global standardized ultrasound diagnostic DVT protocol, is needed in order to maximize the potential of this important diagnostic tool, not only to optimize the related therapeutic strategy but also to offer a reliable picture of the real incidence of the disease. A careful cost-effectiveness analysis should be made to evaluate the real need for duplex ultrasound scanning, in view of the enormous number of requested scans, often without proper indication.

### **KEY MESSAGES**

- Proper global standardization of lower limb venous hemodynamics assessment is missing in international guidelines.
- Perforating veins incompetence definition is not taking into consideration the net flow direction.
- A proper definition of the minimum required training for ultrasound users is missing, so delivering heterogeneous quality data related to an operator-dependent assessment.
- Validated tests for venous obstruction quantification are missing.
- A globally accepted protocol for lower limb venous thrombosis screening is still missing.

### **SUGGESTED RESEARCH TOPICS**

- Impact of different ultrasound settings in proper flow assessment in a hemodynamic lab.
- Perforating veins net flow direction relationship with diastolic flow assessed by multigate analysis.
- Identification of ultrasound tests for venous obstruction quantification.
- Creation of a globally accepted protocol for deep and superficial venous thrombosis screening.
- Report of hemodynamic data that must be assessed in a correct ultrasound investigation for homogeneous assessment, in particular of superficial venous system reflux recurrence analysis.<sup>33-37</sup>

- Identification of a cost-effective protocol for lower limb ultrasound venous screening in chronic venous disease.

## **2. ENDOVENOUS SAPHENOUS ABLATION**

### **MAIN TOPICS**

- Thermal Tumescient devices
- Non Thermal Non Tumescient devices
- Endovenous Heat Induced Thrombosis
- Thrombo-prophylaxis in superficial endovenous procedures

### **ANALYSED GUIDELINES**

- **AUSTRALIA 2010:** Australasian College of Phlebology.<sup>38</sup>
- **USA 2011:** Society for Vascular Surgery (SVS) and the American Venous Forum (AVF).<sup>2</sup>
- **GLOBAL 2012:** International Union of Phlebology (UIP).<sup>39</sup>
- **UK 2013-2016:** National Institute for Health and Care Excellence (NICE).<sup>40</sup>
- **EUROPE 2015:** European Society for Vascular Surgery (ESVS).<sup>6</sup>
- **USA 2016:** American Vein & Lymphatic Society (AVLS), former American College of Phlebology (ACP).<sup>41</sup>
- **LAT-AM 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>

### **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

Thermal tumescent saphenous ablation (TT) is recommended as first treatment choice for great saphenous vein (GSV) insufficiency in all the analysed documents, yet the grade of evidence varies significantly among the documents. On this topic it should be noted that AVF/SVS 2011 document was a pioneering one and currently in process for an imminent update publication.<sup>2</sup>

AVF/SVS 2011 recommended them with a 1B,<sup>2</sup> while the UIP 2012 document upgraded them to 1A<sup>3</sup> as the ESVS 2015 did.<sup>6</sup> Yet, in 2016, AVLS guidelines gave a 1B indication to TT,<sup>42</sup> while, always in 2016, Latam guidelines gave a 1A to endovenous laser ablation and 1B to radiofrequency<sup>8</sup> (Fig. 2.1).

Interestingly, even more variability is associated with the indications for small saphenous vein treatment. While AVF 2011 recommend a high ligation with invagination stripping with a 1B grade,<sup>2</sup> in the following year the UIP document indicates TT as the recommended treatment with a 1A grade.<sup>39</sup> Yet, in 2015, ESVS guidelines reported the same recommendation as 2B.<sup>6</sup> The following year AVLS guidelines reported the recommendation to be 1B,<sup>42</sup> while Latam guidelines didn't mention laser, rather radiofrequency ablation, assigning a 1C evidence to it.<sup>8</sup> In 2013 NICE guidelines are considering all the saphenous axis together, without making a specific analysis of the small vs the great saphenous vein (Fig. 2.2).<sup>40</sup>

Innovative Non Thermal Non Tumescent (NTNT) devices have been recently introduced in the international guidelines. Yet a significant discrepancy can be noted in the different grade of evidence assignment. Both NICE 2013<sup>40</sup> and ESVS 2015<sup>6</sup> are reporting the need of more investigations on cyanoacrylate ablation before providing any recommendation, while Latam 2016 guidelines are recommending cyanoacrylate ablation with a grade 1C.<sup>8</sup> The same need of further investigation was reported for Mechano-chemical ablation (MOCA) with Clarivein according to ESVS 2015,<sup>6</sup> while the following year NICE<sup>40</sup> included this procedure among the recommended ones for saphenous reflux treatment. Always in 2016, AVLS<sup>6</sup> and Latam guidelines<sup>8</sup> differed in the recommendation grade, assigning a 2B and 2A respectively. AVF/SVS 2011 recommended powered phlebectomy with a 2C,<sup>2</sup> while NICE is currently stating that evidence does not appear adequate to support this procedure,<sup>40</sup> in accordance also with ESVS 2015.<sup>6</sup> To the contrary, the same procedure has a 2C recommendation according to Latam 2016,<sup>8</sup> where also steam ablation is reported as 2C (the only guideline reporting about steam ablation) (Tab2.1, Fig. 2.3).

	Australia 2010	USA-AVF 2011	Global UIP 2012	UK-NICE 2013	Europe ESVS 2015	USA AVLS (ACP) 2016	LATAM 2016
GLUE	X	X	X	Under evaluation	Need more investigations	X	(2C)
MOCA	X	X	X	Accepted as standard (2016)	Need more investigations	Mechanochemical ablation (Clarivein Device) may also be used to treat truncal venous reflux (2B)	Clarivein (2A)
OTHER TREATMENTS	X	Powered phlebectomy as an alternative to traditional phlebectomy for extensive varicose veins (2C)	X	Powered phlebectomy Evidence does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research.	Steam and Powered phlebectomy: need more investigation	X	Steam (2C) TRIVEX (2C)
<b>GLUE IS 2C (LATAM), UNDER EVALUATION IN NICE AND EUROPE  MOCA IS 2A (LATAM), 2B (ACP-AVLS), ACCEPTED IN NICE AND EUROPE</b>							

**Tab. 2.1: International recommendations for Non thermal Non tumescent saphenous ablation recommendations.** Both NICE 2013<sup>40</sup> and ESVS 2015<sup>6</sup> are reporting the need of more investigations on cyanoacrylate ablation before providing any recommendation, while Latam 2016 guidelines are recommending cyanoacrylate ablation with a grade 1C.<sup>8</sup> The same need of further investigation was reported for Mechano-chemical ablation (MOCA) with Clarivein according to ESVS 2015,<sup>6</sup> while the following year NICE<sup>40</sup> included this procedure among the recommended ones for saphenous reflux treatment. Always in 2016, AVLS<sup>6</sup> and Latam guidelines<sup>8</sup> differed in the recommendation grade, assigning a 2B and 2A respectively. AVF/SVS 2011 recommended powered phlebectomy with a 2C,<sup>2</sup> while NICE is currently stating that evidence does not appear adequate to support this procedure,<sup>40</sup> in accordance also with ESVS 2015.<sup>6</sup> To the contrary, the same procedure has a 2C recommendation

according to Latam 2016,<sup>8</sup> where also steam ablation is reported as 2C (the only guideline reporting about steam ablation).

Another discordance among guidelines can be found in the indication of performing the tributary treatment at the same time of the saphenous ablation. In 2011 AVF/SVS stated that staging was not making a difference, unless general anesthesia was used: in this last case staging is recommended (grade 1B).<sup>32</sup> Two years later, NICE recommended to perform the tributary treatment at the same time of the saphenous ablation<sup>40</sup> an indication confirmed by ESVS in 2015 with a grade IIB.<sup>6</sup> All the other analysed guidelines are not providing staging indications. Disagreement can be found also in the contraindications: while the Australian 2010 document is considering an acute SVT and an infection as a relative contraindication,<sup>38</sup> the UIP 2012 consider the same conditions as absolute contraindications.<sup>39</sup> While NICE is considering the great saphenous vein extra-fascial location as a possible contraindication to TT,<sup>40</sup> the other guidelines are not taking this aspect in consideration, with the exception of Latam 2016 reporting tortuosity and vessel diameter as relative contraindications.<sup>8</sup> No other guidelines apart Latam 2016 mention the vessel caliber as a contraindication.<sup>8</sup>

Endovenous heat induced thrombosis (EHIT) is variably described among the guidelines too. The only ones reporting about it are the AVF 2011,<sup>2</sup> UIP 2012,<sup>39</sup> NICE 2013,<sup>40</sup> ESVS 2015.<sup>6</sup> While AVF/SVS 2011 is recommending with a grade 2C post-procedural ultrasound scanning within 24 to 72 hours to exclude thrombotic complications,<sup>2</sup> UIP 2012 states more evidence is needed before formulating recommendations.<sup>39</sup> ESVS 2015 simply states that, whenever EHIT extends into the common femoral vein, it has to be treated as deep vein thrombosis.<sup>6</sup> AVF is completing now a document dedicated to EHIT management and its publication is planned for the end of 2019.

From the analysis of the literature, no defined agreed EHIT management strategy can be found.

In the same way, no univocal indications can be found in the guidelines regarding post endovenous thermal procedures thrombo-prophylaxis. While Australia 2010,<sup>38</sup> AVF/SVS 2011<sup>2</sup> and UIP 2012<sup>39</sup> are recommending against routine prophylaxis, only the last one reports a specific grade of recommendation

(1C).<sup>39</sup> On the other side, in 2015, ESVS guidelines stated that more studies are necessary before formulating recommendations<sup>6</sup> and in 2016 Latam guidelines indicate thrombo-prophylaxis with anticoagulation, but just for laser procedures and for under 40 female using hormonal therapy, for patients with heart/renal disease and in case of coagulation disorders.<sup>8</sup>

## **SIGNIFICANT RECENT DATA RELATED TO THE MEETING DISCUSSION**

### **1-2. Thermal and not Thermal ablation**

In 2017 a meta-analysis related to great saphenous vein procedures with >5 years follow up reported that EVLA with and without ligation and high ligation with stripping (HL+S) had better anatomical success rates than ultrasound guided foam sclerotherapy (UGFS) (34% vs 88%, 88%, 83% respectively, P<.001). VCSS scores were not significantly different following EVLA and HL+S.<sup>42</sup> In 2018 a retrospective analysis on 1811 RF and EVLA procedures reported no significant differences between occlusion rates of the two devices. EHIT was reported in 5.9% of cases, but, excluding the type 1, the percentage dropped down to 1.6%. EVLA was associated with a higher rate of thrombotic complications compared to RF (11.4% vs 7.7%, P=.007).<sup>43</sup> No significant difference in occlusion rates, VCSS, AVQQ and median time to return to work were reported between RF and EVLA at 5 years also in another 2018 prospective comparative cohort study.<sup>44</sup> Always in 2018, it was pointed out how TT discomfort is mainly associated with the tumescent infiltration rather than the device itself, thus making the NTNT option appealing even if yet requiring proper validation in the comparison with TT.<sup>45</sup>

In 2017, the American Vein & Lymphatic Society (formerly American College of Phlebology), published a consensus document on the anterior accessory saphenous vein indicating RF or EVLA or ultrasound-guided foam sclerotherapy to treat symptomatic incompetence (Grade 1C).<sup>46</sup>

In 2016, Bozkurt compared EVLA with a new cyanoacrylate reporting no significant difference in occlusion rates, with a faster procedural time and a smaller peri-procedural pain following glue use.<sup>47</sup> In 2017, a systemic review on MOCA with Clarivein analysed the data coming from 1521 treatments, reporting an 87% occlusion rate at 3 years, concluding that the technique is an effective GSV treatment,

but with clinical results dropping over time.<sup>48</sup> In 2018 the 2 years follow up comparison between RF and cyanoacrylate was published, reporting no significant differences in terms of occlusion rates (95.3% vs 94%), symptoms and quality of life.<sup>49</sup> A randomized comparative trial comparing MOCA and RF demonstrated less post-operative pain with MOCA, but more hyperpigmentation compared with RF. MOCA has also been associated with more anatomic saphenous recanalizations, yet with a faster improvement in VCSS compared to RF. These data point out the potential bias of the differently performed tumescent anesthesia, potentially impacting the peri-operative pain, while they also highlight the relative importance of the anatomical failure in relation to the clinical improvement. Indeed both MOCA and RF showed overlapping clinical results at 2 years.<sup>50</sup> The same concept is sustained by a recent publication comparing MOCA with EVLA and RF and showing that the great saphenous vein occlusion at 1 year is significantly higher with EVLA and RF compared to MOCA, but with no significant differences in the quality of life among the three procedures.<sup>51</sup>

An abstract reporting just 6 months follow-up results of a randomized comparative trial involving MOCA and EVLA showed no significant differences in terms of anatomical success, with a better procedural and post-procedural pain control following MOCA.<sup>52</sup> In 2018, 1 year follow up data were reported following MOCA Flebogrif technique, in 172 GSV and 28 SSV treatment, with an occlusion rate of 92%.<sup>53</sup> As reported in a systematic review in 2017, looking at the evidence based data on MOCA and glue, these new techniques are promising as alternative TT, but still requiring high-quality randomized trial assessing their performance in comparison with well-established procedures.<sup>54</sup> In conclusion, a randomized clinical trial involving cyanoacrylate, RF and EVLA showed no significant difference at 2 years (cyanoacrylate 92.6%, RFA 90.9%, and EVLA 91.5%,  $p = .89$ ). Peri-procedural pain was lower using glue, but complication rate was similar among the 3 techniques. VCSS score was lower at 6 months and 2 years in the glue group ( $P < .001$ ).<sup>55</sup> In terms of staging eventual phlebectomies, in 2016, simultaneous RF ablation and transilluminated powered phlebectomy vs staging the same procedures demonstrated better outcomes in terms of VCSS.<sup>56</sup> In 2017, a literature review pointed out the better short-term and better to equivalent long-term results of combined endovenous saphenous



ablation and phlebectomy.<sup>57</sup> The analysis of the most recent publications also showed that chronic venous insufficiency treatment should not be held just because of age.<sup>58</sup>

A recent publication compared cyanoacrylate glue and EVLA demonstrating a faster procedural time and less periprocedural pain in the glue group, with no significant difference in the occlusion rate and in the quality of life. It should be noted that the follow-up was of only 1 year.<sup>59-60</sup>

### **3. EHIT**

The analysis of 6707 TT procedures showed a EHIT incidence of 3%, with pulmonary embolism in just 0.03% of cases.<sup>61</sup> In 2017, the comparison between TT procedures performed in anticoagulated vs not anticoagulated patients showed just a minor difference in terms of EHIT incidence: 0.3% vs 0.9% at 3 days respectively (P=.016).<sup>62</sup>

### **4. DVT prophylaxis in TT procedures**

The lack of significant evidence on the DVT prophylaxis after TT procedures was nicely pointed out by Nyamekye in 2018. The author also stressed out the difficulty in realizing a proper investigation on the topic considering the extremely rare occurrence of thrombo-embolic events following these procedures.<sup>63</sup>

## **DISCUSSION**

Superficial chronic venous disease treatment has been enriched with a significant number of new technical options in the last 2 decades. Yet, clear indications and related global homogeneity is still lacking in the literature. A major point to look at in the future investigations is the need of a proper risk stratification by means of dedicated scores.

Another major missing point is the duration of the anticoagulation in case the prophylaxis has been indicated. As demonstrated by Sweetland, the post-operative risk of a day-case procedure stays raised up to 10 times for the post-operative following 6 weeks, so making the single shot prophylaxis potentially

inefficient.<sup>64</sup> Currently, at least 1 week of anticoagulation is suggested for patients at risk. Yet, according to Goodyear, in patients at high risk such as the ones with previous DVT or known thrombophilia, a prophylaxis lasting up to six weeks should be taken into consideration.<sup>64</sup>

Proper reports comparing the performance of different devices and techniques in large or extremely superficial refluxing saphenous axis are still missing,<sup>66</sup> together with detailed analysis of the several possible histologic consequences of thermal ablation.<sup>67-69</sup> On the histology topic, two interesting papers showed that radial fibers don't damage the wall by contact, rather by a deep uniform coagulation injury, proportional to the energy level.<sup>70,71</sup> In case of holmium laser use, a hyalinization process has been demonstrated, with endothelium lining sparing and media elastic fibers fragmentation.<sup>72</sup> Another major, usually underestimated, topic in saphenous incompetence treatment is the cost-effectiveness, particularly considering the almost overlapping performance of the different devices. In UK, a recent cost-analysis considered radiofrequency as the most cost-effective one, followed by MOCA, EVLA, HL+S, glue and foam.<sup>73</sup>

In case of ulceration, the most cost-effective approach resulted to be surgical vs just compression, while not enough data regarding the other techniques are available.<sup>74</sup>

A detailed cost-effectiveness analysis should also include the EHIT sonographic surveillance and the real clinical need of it, considering the extremely low incidence of this complication. A major step forward must be taken in future researches by identifying the most meaningful post-procedural key outcome measures, so to provide homogeneous data collections. Indeed occlusion rates and hemodynamics parameters require integration with quality of life measurements. Yet only AVVQ, CIVIQ and VEINES-QoL/Sym are considered thoroughly validated, with the AVVQ and CIVIQ having been investigated just by their creators with involvement of just local populations. Only with proper technical and patients reported outcome will be possible to objectively quantify the success of the indicated procedure.<sup>75</sup> In 2018 data showed that comparison of different techniques without including specific hemodynamic details, such as the incompetence of the ilio-femoral tract, could lead to the bias of a heterogenous assessment, thus stressing the importance of both a sonographic and clinical proper

report.<sup>76</sup> This concept has been properly highlighted in a 2019 editorial, requesting proper endovenous registry and uniform data collection.<sup>77</sup>

### **KEY MESSAGES**

- International recommendations in endovenous saphenous ablation are heterogeneous, particularly for Small Saphenous Vein treatment.
- Thrombo-prophylaxis after endovenous procedures is lacking evidence-based international recommendations.
- International recommendations in EHIT management are sparse and heterogeneous.
- Different techniques for saphenous ablation are not compared in homogeneous reflux patterns, so introducing potential bias.

### **SUGGESTED RESEARCH TOPICS**

- Small Saphenous Vein and Anterior Accessory saphenous vein endovenous ablation techniques.
- Perioperative thrombo-prophylaxis in endovenous saphenous ablation.
- EHIT management.
- Homogenous reflux pattern analysis for different endovenous techniques comparison.
- Cost-effective analysis of the different procedures, based not just on anatomical occlusion rates, but also on patient reported outcomes.

## **3. BANDAGING, ADJUSTABLE COMPRESSION WRAPS, INTERMITTENT PNEUMATIC**

### **COMPRESSION**

#### **TOPICS**

- Bandaging in venous ulcer
- Adjustable compression wraps (ACW)

- Intermittent Pneumatic Compression (IPC)

### **ANALYSED GUIDELINES**

- **USA 2014:** Society for Vascular Surgery and the American Venous Forum (SVS/AVF).<sup>32</sup>
- **EUROPE 2015:** European Society for Vascular Surgery (ESVS).<sup>6</sup>
- **ITALY 2016:** Italian society of Phlebology-Italian Society of Vascular and Endovascular Surgery (SIF-SICVE).<sup>78</sup>
- **LATIN AMERICA 2016:** Guías latino americanas de terapéutica para la patología venosa.<sup>8</sup>
- **UK 2018:** NICE guidelines.<sup>79</sup>
- **EUROPE 2018:** Indications for medical compression stockings in venous and lymphatic disorders.<sup>80</sup>
- **GLOBAL 2018:** European Venous Forum (EVF), International Union of Angiology (IUA), Cardiovascular Disease Educational and Research Trust, International Union of Phlebology (UIP).<sup>11</sup>
- **GERMANY 2018:** Guidelines on intermittent pneumatic compression. German Society of Phlebology.<sup>81</sup>
- **USA 2019:** Compression therapy after invasive treatment of superficial veins.<sup>82</sup>

### **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

#### **1. Bandaging in ulcer care**

In all the analysed guidelines no definitive data indicated the superiority of a bandaging technique over another (spiral, figure of eight, circular).

The AVF/SVS 2014<sup>32</sup> guideline indicated superiority of multicomponent compression bandage over single component for venous ulcer treatment with a grade 2B recommendation, yet the 2016 Latam<sup>8</sup> guidelines pointed out that there was no evidence supporting a compression modality over another. The 2018 UIP/IUA/EVF<sup>11</sup> document supported the use of multicomponent vs single component bandages, yet, in the same year, NICE<sup>79</sup> recommended to tailor the bandaging modality to the patient, favouring 2-layer vs 3-4-layer bandage, since the 2-layer system was more practical in mobile subjects. In 2019, the

SVS/AVS/AVLS document supported once again the multilayer option.<sup>82</sup>

The SVS/AVF 2014<sup>32</sup> recommendation graded the role of compression in reducing the ulcer recurrence risk as grade 2B. The following year ESVS reported a 1B indication for the same venous ulcer recurrence risk reduction.<sup>6</sup> One year later, Latam reported a 1A<sup>8</sup> recommendation on the same topic. No significant literature was found to justify such upgrade. The recommendation for compression in ulcer recurrence reduction was scored as 1A also by the European guideline in 2018<sup>80</sup> (Fig. 3.1).

The 2019 SVS/AVF<sup>82</sup> guideline recommended not to use compression whenever ankle pressure was less than 60 mmHg (grade 2C), in accordance with the 2014 guideline.<sup>32</sup> Nevertheless, despite the time lapse, the recommendation level has remained 2C.

The European 2018 guideline<sup>80</sup> reported a minimum systolic ankle pressure of 70 mmHg rather than 60 mmHg, but no specific recommendation grade was provided.

## **2. Adjustable compression wraps (ACW)**

ACW has been reported as a possible alternative since the SVS/AVF 2014<sup>32</sup> guideline report. The 2015 NICE reported that Juxta Cure use was associated with a reduction in wound size, healing rate and quality of life improvement.<sup>83</sup>

In the same year, ESVS<sup>6</sup> stated that ACW represented a viable alternative to traditional bandaging and that adding an elastic component seemed to be more effective.

In 2018, the UIP/IUA/EVF guideline<sup>11</sup> included ACW, pointing out its higher safety profile compared to an elastic bandage. The same was reported in the SVS/AVF 2019 document.<sup>82</sup>

## **3. Intermittent Pneumatic Compression (IPC) in addition to compression therapy**

The SVS/AVF 2014<sup>32</sup> guideline recommended IPC in venous ulcer treatment with a grade 2C recommendation in patients where other compression options were not available or had failed.

The following year ESVS<sup>6</sup> provided a 1A recommendation in its use for symptomatic relief in C3-C6 chronic venous disease patients for whom standard methods were not indicated or had failed. A 6

months period with standard methods was recommended with a IIaB level of evidence. The SVS/AVF/AVLS 2019<sup>82</sup> document recognized a key role of IPC in correcting elevated venous pressure in ulcer patients.

According to the NHS 2017 “Intermittent Pneumatic Compression Therapy Guide”, a protocol of 30 min to 1 hour twice per day at 30-50 mmHg should be used for venous ulcer patients, while for lymphedema the time range should be between 30 min and 2 hours, 2-4 times per day, at 40-60 mmHg.<sup>84</sup>

According to the 2018 German Guideline,<sup>81</sup> in case of venous ulceration, the protocol was of at least 1 hour per day, at least 3 times per week, at 40-50 mmHg.

While the UIP/IUA/EVF 2018<sup>11</sup> document reported that there is some limited evidence that IPC may improve ulcer-healing when added to compression bandages, the German guidelines,<sup>81</sup> in the same year, highlighted this benefit, specifying that its effect is particularly evident in immobile patients, with edema and morbid obesity.

Already back in 2010 Lee BY demonstrated the anti-coagulation effect associated with IPC at the lab evaluation by thromboelastography.<sup>85</sup>

Yet these guidelines are not commenting the eventual need of adding IPC to the standard anticoagulation. The same indication is given by the American College of Chest Physicians for non surgical critically ill patients, but just with a grade 2C.<sup>86</sup>

### **SIGNIFICANT NEW DATA RELATED TO THE MEETING DISCUSSION**

As pointed out in a recent publication by Mosti,<sup>87</sup> compression offers an example of the fragility of the currently available so called “evidence-based data”. Indeed, even if compression is considered a key in chronic edema treatment, specific data regarding materials, pressure levels and protocols are either lacking or sparsely provided.

The real need of high pressure levels for edema management is questionable, leaving the possibility to control edema with lower compression levels.<sup>88</sup>

On the other side, it was demonstrated that interface pressure of around 40 mmHg can effectively reduce chronic edema, while allowing good patient compliance by means of ACW use.<sup>89-90</sup>

In terms of edema treatment, 23-32 mmHg graduated compression stockings and elastic kits demonstrated to be almost as effective as rigid bandaging.<sup>91-93</sup>

Back in 2012 it was demonstrated that arterial impairment was not a contraindication to compression therapy. It could actually be beneficial by using short stretch bandaging not exceeding a 40 mmHg resting pressure, once a proper patient evaluation and ankle-brachial index (>0.5) determination have been done.<sup>94</sup>

This aspect was recently pointed out also with short stretch bandaging in mixed-ulcers.<sup>95</sup>

Looking at the venous ulcer healing, in 2018 a meta-analysis evaluated 1437 patients reporting no significant difference between 4 layer and 2 layer bandaging.<sup>96</sup>

Going back to the 2012, Cochrane review on compression for ulcer stated that, increases healing, multicomponent systems are more effective than single-component, particularly if containing an elastic bandage. Moreover, two components seem to perform as well as 4 component and high-pressure graduated stockings demonstrated to be associated with a better result than short stretch bandages.<sup>97</sup>

Yet, in 2015, as already reported also by the same Cochrane analysis, Partsch pointed out that these results are confounded by the skill and experience of the bandagers and that proper assessment of interface pressure and stiffness should be included for data homogeneity.<sup>98</sup>

Back in 2005, Blecken and Villavicencio reported the superiority of ACW compared to a 4 layer elastic bandage in ulcer healing.<sup>99</sup>

A prospective randomized comparative trial compared ACW versus inelastic multi-component bandages for leg lymphedema, demonstrating a significantly more pronounced reduction in volume in favor of ACW, with an improvement in clinical outcome associated with the autonomous handling of the compression.<sup>91</sup> The potentials of ACW in edema management have been recently pointed out in the 2018 Benigni investigation reporting the superiority of this compression option in lower limb volume

reduction, compared to short stretch bandage.<sup>100</sup> The effectiveness of ACW in edema management compared to the multilayers compression bandages was reported this year also at the upper limb level.<sup>101</sup> IPC has demonstrated its effectiveness in lower limb volume reduction too<sup>102</sup> and recently it also demonstrated its potential use in preventing minor amputations for arterial disease, with a significant improvement in rest pain and amputation-free survival.<sup>103,104</sup>

A just published investigation reported how both sequential and single-compartment compressions are able to increase tissue oxygenation, with a significantly higher effect using the multi-chamber device.<sup>105</sup> On the thrombo-embolism side, in 2016 Cochrane<sup>106</sup> analysis showed a benefit in adding IPC to pharmacological thrombo-prophylaxis in high risk trauma and surgical patients, while, in 2019, New England Journal of Medicine underlined no significant benefit in adding IPC in critically ill patients already covered by drugs for venous thrombo-prophylaxis.<sup>107</sup>

## **DISCUSSION**

All the current recommendations in compression are properly based on the GRADE system. Yet, future investigations should focus on sound data, so to avoid a lot of redundant work and inappropriate grading.

For example, comparing 1 and 3 weeks of thrombo-prophylactic stockings (<20 mmHg) use after venous surgery<sup>108</sup> or comparing thrombo-prophylactic stockings with no compression after foam sclerotherapy at the thigh<sup>108</sup> has been considered a minor evidence, based on the fact that the pressure level is too low. Considering these evidence as valuable inside the GRADE leads to the risk of inappropriate recommendations.

Another example is offered by the SOX trial whose results downgraded the recommendation of graduated elastic stocking for post-thrombotic prevention abruptly in the grading system, despite the multiple bias included in the investigation, such as the delayed use of compression, the lack of proper compliance assessment, the use of placebo stockings that could have actually had an effect on edema and inflammation and the use of different anticoagulants.<sup>110,111</sup> The importance of knowing the



compression dose and mode becomes particularly evident when analysing multicomponent bandages that are usually erroneously considered elastic, while actually inelastic at the stiffness measurement.<sup>112</sup>

There are two main compression effects: edema and inflammation reduction on one side and a hemodynamic effect on the other side. A hemodynamic effect requires a vein narrowing, which requires a high pressure. Edema reduction can be obtained also with minor pressure.

Future guidelines should specify the dose and mode (stiffness) of compression. The dose of the resting pressure can be low (<20 mmHg), medium (20-40 mmHg) or strong (40-60 mmHg). The compression mode, expressed as static stiffness index (SSI), related to working pressure can be expressed as elastic (SSI<10) or rigid (SSI>10).<sup>113,114</sup>

The involved experts of this session pointed out the need of having future investigations reporting at least the interface pressure measurement at B (ankle behind the inner malleolus) and B1 (tendinous part of the medial gastrocnemius muscle turns into the muscle), the static stiffness index in B1 and the compliance assessment. Compliance report remains a main issue to be solved in compression science and the use of properly validated devices to measure both interface pressure and compliance is strongly recommended by the panel.

Last but not least, the panel points out that a careful analysis of the current contraindications to compression should be performed. Indeed current contraindications such as arterial impairment can actually represent good indication in properly identified clinical scenarios, as reported in the above mentioned literature.

Specifically considering IPC, the literature analysis underlines the need of proper standardization for the used protocols and related devices. Moreover, concerns have been already reported regarding the proper use of the same devices. In 2002 Corwell for example demonstrated that only 19% of trauma patients were using IPC properly,<sup>115</sup> while Maxwell data pointed out up to 52% cases of IPC misuse.<sup>116</sup> Thus, a proper standardization of the protocols and of the devices, together with a reliable patient compliance assessment, is highly needed in order to assess the clinical and health-costs benefits associated with IPC use.

Cost-effectiveness seems to be a potential significant benefit in the use of ACW, with preliminary evidence suggesting a saving of 61.88 £ per week compared to bandage in wound care management.<sup>117</sup>

Despite ACW interface pressure measurement have been already reported,<sup>91,118</sup> it's fundamental to have future investigations including this data, together with the associated stiffness index, so to better understand both the compression pathophysiology and the potentials of the same device, moreover guaranteeing homogenous data comparison.

Indeed, the main issue with different compression modalities comparison remains the lack of report of the same compression dose (interface pressure measurement) and mode (stiffness). Empirically, world renowned experts agree that all the compression modalities, including bandaging, ACW, IPC and graduated elastic stockings are of great benefit for the patient and need to be properly known by the healthcare professionals. At the same time, future investigations need to be properly designed, including assessments of compression features, so making the data valid in term of homogeneity, standardization and reproducibility.

### **KEY MESSAGES**

- The lack of compression dose specification (interface pressure measurement) represents a major bias in the current literature.
- No clear recommendations are provided in favour of one type of bandage over another and/or over other modalities of compression.
- International guidelines are recognizing safety and efficacy of adjustable compression wraps.
- Intermittent pneumatic compression demonstrated anti-coagulation effect in the lab, but guidelines are not commenting on the need of adding it to standard anticoagulation.

### **SUGGESTED RESEARCH TOPICS**

- Randomized trials comparing bandaging, adjustable compression wraps and intermittent pneumatic compression.

- Randomized trials comparing different intermittent pneumatic compression protocols.
- All the future research in compression should include the report of the assessed interface pressure in B (ankle point of minimum girth) and B1 (area at which the Achilles tendon changes into the calf muscles) points, together with the static stiffness index, so to avoid heterogeneous compression doses comparisons.

#### **4. GRADUATED ELASTIC STOCKINGS**

##### **TOPICS**

Graduated elastic stockings (GCS) compression in:

- Venous symptoms & signs control
- Ulcer healing and recurrence
- Venous thrombosis
- Post-procedural
- Flying/Long travel
- Pregnancy

##### **ANALYSED GUIDELINES**

- **USA 2011:** Society for Vascular Surgery and the American Venous Forum (SVS/AVF).<sup>2</sup>
- **UK 2013:** NICE guidelines.<sup>40</sup>
- **EUROPE 2015:** European Society for Vascular Surgery (ESVS).<sup>6</sup>
- **LATIN AMERICA 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>
- **GLOBAL 2018:** European Venous Forum (EVF), International Union of Angiology (IUA), Cardiovascular Disease Educational and Research Trust, International Union of Phlebology (UIP).<sup>11</sup>

- **EUROPE 2018:** Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement.<sup>80</sup>
- **USA 2019:** Compression therapy after invasive treatment of superficial veins.<sup>82</sup>

## **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

### **1. Venous symptoms and signs control**

NICE<sup>40</sup> recommends not to offer GCS to treat varicose veins, unless interventional treatment is unsuitable. Interestingly, this British indication is the opposite practice than the one followed in USA<sup>119</sup> where at least 3 months of GCS use are requested before being eligible for an interventional treatment.

Even more interestingly, according to the same USA AVF/SVS 2011 guidelines, compression is recommended (Grade 2C) as therapy for symptomatic varicose veins, but not as the primary treatment if the patient is candidate for saphenous ablation (Grade 1B).<sup>2</sup>

Both the British and American indications represent an indirect recognition of the still beneficial use of GCS compared to no use in case of procedural unfeasibility and evitability, respectively.

ESVS 2015<sup>6</sup> document recommends GCS as definitive treatment in patients who can not be operated, with a grade 2bC, so agreeing with NICE indication.<sup>40</sup>

GCS use in venous disease symptoms control has been recommended with a grade 2C from AVF/SVS 2011,<sup>2</sup> while it was significantly upgraded to 1B from 2015 ESVS<sup>6</sup> and 2018 European<sup>80</sup> guidelines.

These last ones extended the indication of GCS use for venous symptoms control not just for varicose veins patients, but also for healthy individuals at risk of swelling.

Latin America guidelines<sup>8</sup> are the only ones giving indications to different compression levels, based on CEAP classification and on varicose veins diameter.

European 2018<sup>80</sup> guidelines recommend GCS also for improvement of skin changes such as lipodermatosclerosis with a grade 1C.

## **2. Ulcer healing and recurrence**

In 2011 AVF/SVS<sup>2</sup> recognized a grade 1B to compression in ulcer healing. In 2015 ESVS<sup>6</sup> graded the same indication always as 1B, but specifying the use just of bandages, while, in 2018, the European guidelines reported a 1A.<sup>80</sup> The following year, SVS/AVF/AVLS went back to a 1B for the same indication.<sup>82</sup>

Latin America guidelines<sup>8</sup> points out the importance of compression in general for ulcer healing, including both bandaging and 30-40 mmHg GCS, with no specific grade of recommendation.

The pressure level was reported also by ESVS 2015,<sup>6</sup> but at the higher level of at least 40 mmHg.

AVF/SVS 2011<sup>2</sup> and European 2018 guidelines<sup>80</sup> recognize a 1A indication to compression for ulcer recurrence prevention. Interestingly, SVS/AVF/AVLS 2019 document downgraded this evidence to 1B.<sup>82</sup>

## **3. Venous thrombosis**

For venous thrombo-prophylaxis, NICE guidelines recommend the use of GCS with a calf pressure of 14-15 mmHg, day and night, in hospitalized patient until hypomobility is over.<sup>120</sup>

Asian 2017<sup>121</sup> guidelines didn't recommend GCS for thrombo-embolism prophylaxis in medically ill patients, while European 2018 guidelines<sup>80</sup> indicate the use of GCS for prophylaxis in patients undergoing surgery with a grade 2C, increasing the indication to 2B in case anticoagulation is contraindicated.

The same European document recommends GCS use in acute deep venous thrombosis for reducing pain and swelling with a grade 1B, while for superficial venous thrombosis the recommendation has a 1C grade.<sup>80</sup>

In 2016, the American College of Chest Physicians recommended not to offer GCS for PTS prevention after a proximal DVT, unless thrombosis is symptomatic (grade 2B).<sup>122</sup>

NICE in 2015 recommended not to offer GCS to prevent post-thrombotic syndrome or thrombotic recurrence after a proximal DVT.<sup>123</sup>

Malaysian 2013 guidelines recommend 23 mmHg GCS for 2 years in case of proximal DVT, specifying to wear it starting from 1 week after diagnosis or when swelling is significantly reduced.<sup>124</sup>

An update of these guidelines is expected by December 2019.

Australian, German, French and Dutch guidelines are still confirming the GCS use after DVT for PTS prevention.<sup>125-128</sup>

#### **4. Post-procedural**

AVF/SVS 2011<sup>2</sup> document indicates the use of GCS to reduce hematoma, pain, swelling after open venous surgery with a 1B grade. A period of 1 week for C2 patients is specified. In 2015 ESVS upgraded post-operative compression after superficial venous surgery, endovenous truncal ablation and sclerotherapy with a grade 1A.<sup>6</sup>

Three years later, European 2018<sup>80</sup> guidelines recommended the use of post-operative GCS with a grade 1B. Following sclerotherapy, the document specifies that 23-30 mmHg for 3 weeks are recommended for better aesthetic result, with a grade 2B.

In 2019, AVF/SVS/AVLS dedicated an entire document to post-operative compression.<sup>82</sup> The main indications are to use GCS after thermal tumescent or stripping techniques (grade 2C), using at least 20 mmHg and possible eccentric (grade 2B). The duration of the compression is left at the clinical judgement, while, after sclerotherapy, the recommendation grade differs from the 2018 European document<sup>80</sup> moving from 1B to 2C (Fig. 4.1).<sup>82</sup>

Latin America guidelines<sup>8</sup> suggest a post-operative eccentric compression, but without specifying a grade of evidence.

#### **5. Long distance flights**

In 2011 British Journal of Hematology published guidelines on travel-related venous thrombosis, pointing out that there is no recommendation to global GCS for all the long-distance travellers (grade 1C). At the same time the document indicated that travellers at high thrombotic risk should wear well fitted GCS for longer than 3 hours flights (grade 2B).<sup>129</sup>

The following year, the American College of Chest Physicians indicated the use of 15-30 mmHg GCS for long-distance travellers at increased VTE risk with a grade 2C, while for all other travellers the document recommended against its use (2C).<sup>122</sup>

Despite the single year separating these guidelines from the 2011 British one, recommendations grades changed, actually been downgraded by the most recent indications.<sup>122</sup>

NICE<sup>40</sup> guidelines recommend GCS for all moderate to high risk long-haul travellers.

European 2018 guidelines<sup>80</sup> indicate GCS use in long-lasting flights in patients at risk with a grade 2B. At the same time, the same guidelines recommend with a grade 1B the use of GCS in healthy subjects to prevent leg swelling during prolonged flights.<sup>80</sup>

## **6. Pregnancy**

According to NICE 2013,<sup>40</sup> GCS should be prescribed for symptom relief of leg swelling associated with varicose veins during pregnancy.

In 2015 the Royal College of Obstetricians & Gynaecologists indicated the use of 14-15 mmHg GCS in pregnancy and puerperium for women at thrombotic risk and for those travelling for more than 4 hours.<sup>130</sup>

European 2018 guidelines<sup>80</sup> indicate the GCS use also for healthy subjects at risk of swelling, as pregnant women are, with a grade 1B.

## **SIGNIFICANT NEW DATA RELATED TO THE MEETING DISCUSSION**

### **1. Venous symptoms and signs control**

In 2018 an interesting randomized double blind placebo controlled trial demonstrated that 18-21 mmHg GCS are able to positively impact pain and aching related to venous disease.<sup>131</sup>

In this context, it should be remembered that subjective symptoms are not specific for venous changes and they can also be improved by GCS.<sup>132</sup>

An increasing scientific interest is dedicated to the evaluation of the GCS ability of potentially impacting sport performance and recovery.

In 2018, GCS 20-30 mmHg use during a 10 km amateur run demonstrated to significantly reduce the venous filling index and residual volume fraction, while not significantly affecting the ejection fraction, the capillary lactate values and the heart rate.<sup>133</sup>

In 2017, it was demonstrated that wearing 23 mmHg GCS during an intermittent walk was associated with a significant decrease in lower limb volume and with a decrease in the perceived fatigue.<sup>134</sup>

In 2019, another investigation reported a significant decrease of leg volume and perceived fatigue after using 20-30 mmHg GCS in a 30 minutes standardized continuous walk.<sup>135</sup>

## **2. Ulcer healing and recurrence**

A fundamental paper by Ashby reported the possibility of successfully treating venous ulcers by two-layer GCS rather than four-layer bandage (equally effective in the study). Yet the same investigation focused on GCS use just in a selected group of patients with not wide lesions.<sup>136</sup>

In 2017 the Journal of Critical Care pointed out the importance of proper management for GCS in intensive care units, where not proper use of the garment can of course lead also to pressure injuries.<sup>137</sup>

In the same year Li-Zha published a reply to the same article, pointing out that GCS remain a powerful tool as long as managed by expert hands, particularly in advanced cases like the intensive care unit ones.<sup>138</sup>

An interesting paper was published in 2017 showing that, in patients affected by intermittent claudication, GCS didn't decrease the limb oxygenation and the walking capacity, so pointing out the potential benefit in properly selected mixed ulcer patients.<sup>139</sup>

## **3. Venous thrombosis**



In 2018 Cochrane reported that there is high-quality evidence in GCS DVT prevention in hospitalized patients undergoing general and orthopaedic surgery. Moderate quality evidence support their use to reduce the risk of proximal DVT and low quality evidence in the PE prevention.<sup>140</sup>

Interestingly, differently from the European 2018 guidelines published on Phlebology Journal,<sup>80</sup> in 2018 the European Journal of Anesthesiology published guidelines recommending not to use GCS for prophylaxis even in very high risk patients if pharmacology administration is not contraindicated. The same guidelines pointed out the extreme heterogeneity in different institutions recommendations and the lack of high grade recommendations.<sup>141</sup> In 2018, immediate compression after DVT demonstrated to be associated with a significant reduction of the residual venous obstruction.<sup>142</sup>

After the SOX trial,<sup>110</sup> several meta-analysis pointed out the lack of significant data for proper evidence-based recommendation on GCS use for PTS prevention. In particular homogeneity in data collection and appropriate scoring systems are needed.<sup>143-146</sup>

The 2017 dedicated Cochrane concluded that low-quality evidence support the use of GCS for preventing post-thrombotic syndrome, but it also pointed out that final conclusions on the topic are missing, particularly considering the same post-thrombotic syndrome definition has not globally defined in a uniform way.<sup>147</sup>

In 2018 the IDEAL study demonstrated that individualized therapy with GCS for PTS prevention is non-inferior to standard duration of therapy of 24 months.<sup>148</sup>

#### **4. Post-procedural**

A 2018 review reported no significant difference in extended use of compression after endovenous ablation of varicose veins, in terms of bruising, recovery time, leg swelling. Minor evidence suggested an improvement in quality of life and pain, with a reduction in terms of complication following a longer period of compression use.<sup>149</sup>

In 2019 a dose-effect was reported in post-operative compression, favouring 35 vs 23 mmHg after long-catheter sclerotherapy.<sup>150</sup>

## **5. Flights**

In 2018 it was demonstrated that sitting for 3 hours with GCS versus not GCS use leads to less pain, fatigue, swelling: these data can be considered useful for future investigation in similar on-flight conditions.<sup>151</sup>

## **6. Pregnancy**

In 2016, the French College of Gynaecologists and Obstetricians recommended thrombo-prophylactic use of GCS the morning of the cesarean delivery, maintaining it for 7 days.<sup>152</sup>

In 2017 an investigation showed that 20-36 mmHg can be beneficial in reducing maternal hypotension following epidural analgesia.<sup>153</sup>

A current lack of proper guidelines and thrombo-prophylactic measurements application has been reported in the OBGyn field in 2018.<sup>154</sup>

Use of proper thrombo-embolic risk assessment tools have been recently proposed during pregnancy and puerperium demonstrating their efficacy in proper patient management.<sup>155</sup>

## **DISCUSSION**

European 2018 guidelines reported the indication of GCS use for pain management both in ulcer and thrombotic clinical scenario.<sup>80</sup> Controlling pain onset is fundamental in these cases as a central memory of the experienced pain remains as a lower threshold in the following months.<sup>156</sup>

Delaying the use of proper compression in ulcer or thrombotic patients can negatively impact their following quality of life, also altering the homogeneity of the data in the comparison between GCS users and not users. An example of this can be found in the delayed use of GCS in the SOX trial patients, so altering the assessment of the real benefit of proper compression in symptoms management.<sup>110</sup>

This aspect represents an easily found bias in the literature dedicated to compression, bringing the risk of diluting the validity of the analysed literature.

The importance of timing in compression prescription is reported also in a recently published investigation showing the impact of a properly prescribed compression on residual venous obstruction, pointing out the importance of a not delayed GCS use. The same delay could not only increase the risk of residual venous obstruction,<sup>142</sup> but also impact the pain perception<sup>156</sup> and consequently the related data collection homogeneity. Homogeneity in data collection is a major issue also in post-procedural GCS use. NICE<sup>157</sup> pointed out that the benefit of compression after interventional treatment for varicose veins remains unclear. A well-conducted, multicentre, randomised controlled trial of compression after interventional treatment, including the 3 main interventional treatments (endothermal ablation, ultrasound-guided foam sclerotherapy or surgery), is needed. Each arm should have subgroups for compression type and duration. A compliance and cost-effectiveness analysis should also be included. Moreover, in case the compression is meant to occlude the vein, proper pressure should be applied by wraps, bandages or GCS with additional eccentric compression. A multicentre trial randomising GCS versus no compression for symptomatic varicose veins is needed. The investigation should include quality of life, symptom reduction, and disease progression and compliance assessment. On the other side, future investigations dealing with GCS use during prolonged flights should start from taking into consideration the profound limits present in the literature dedicated to long-haul flying related thrombotic risk. The same definition of long-haul flight is not globally agreed, varying from 3 up to 12 hours and significant heterogeneity is found among the studies reporting the related thrombotic risk. Nevertheless, in 2016 a Cochrane review reported that, in longer than 5 hours flights, patients with at least low thrombotic risk benefit from GCS use for symptomless DVT occurrence. Low quality evidence is reported regarding the GCS ability of reducing edema, mainly because the way edema was measured was poor.<sup>158</sup> Indeed, apart the thrombo-prophylactic benefit, another investigation line should be properly addressed in revealing the real impact of GCS use in prolonged flights for leg edema and related symptoms control. A similar consideration can be done during pregnancy, where usually GCS are prescribed mainly for the eventual thrombo-prophylactic effect, rather than for their positive impact on edema and symptomatology.

Pregnancy is associated with an increased risk of thrombo-embolism of 4 to 6 fold, increasing during the post-partum period, with an absolute risk of 2 out of 1000 pregnant women.<sup>159</sup>

Pregnancy hormonal changes are also associated with an increased tendency toward coagulation, with thrombo-embolism being the first cause of maternal death.<sup>160</sup>

At the same time, a physiological fluid increase is present during pregnancy, so leading to potential edema in up to 8 out of 10 women.<sup>161</sup>

While a GCS role is recognized in pregnancy and puerperium symptoms and thrombotic risk control,<sup>130,162</sup> precise indications in terms of pressure values are lacking, as a proper literature able to provide recommendations with high grade of evidence.

Thrombo-embolism prophylaxis by compression after stroke has been investigated by the CLOT trials without the bias of different anticoagulants use.<sup>163-165</sup> The first investigation showed NO significant benefit in the GCS use (10% DVT rate vs 10.5% in the group with and without compression, respectively; P: ns).<sup>165</sup> Yet, in CLOT II thigh-high GCS were associated with a smaller DVT rate (6.3%) compared to knee-high GCS group (8.8%)(P=0.08).<sup>164</sup> CLOT III demonstrated that intermittent pneumatic compression reduces the DVT risk after stroke from 12.1% to 8.5%.<sup>165</sup> Considering the contradicting data related to compression for stroke patients, future investigations should be performed in a homogenous study population. In conclusion, in general, further research on GCS effect should include objective measurements, always reporting the specific kind of used compression. As described in the session dedicated to bandaging, adjustable compression wraps and intermittent pneumatic compression, reporting the interface pressure in vivo at the B1 point is fundamental to dose the compression. Moreover, reporting also the static stiffness index provides the possibility of homogenous comparison among similar compression modalities. Only a strict methodology in data reporting will be able to bring evidence-based support toward proper clinical practice in compression, so moving forward from empiricism to evidence-based science, maximizing the GCS benefit.

## **KEY MESSAGES**

- All the international guidelines are recognizing an effect of GCS in venous symptoms and signs control, yet with different grade of evidence in their recommendations.
- GCS are globally recognized as useful in venous ulcer recurrence prevention.
- General agreement in GCS use for post-thrombotic symptomatology management is found in international guidelines, while the role in post-thrombotic syndrome prevention is still under debate.
- GCS are recommended post-operatively, but with significantly different evidence among different international guidelines.
- GCS are recommended globally for edema control during prolonged flight, but the minimum needed compression dose is still unclear, as the length of flying requiring proper compression.
- GCS in pregnancy are mainly recommended for symptoms control.
- Preliminary evidence are demonstrating the positive impact of proper compression in healthy subject perceived exertion.

## **SUGGESTED RESEARCH TOPICS**

- Multi-center trial in post-operative compression.
- Investigations in prolonged traveling sitting conditions performed under homogenous conditions.
- Impact of GCS on thrombo-embolism prevention in homogenous populations of pregnant women.
- All future investigations on compression should present a strict methodology, reporting interface pressure and static stiffness measurements.

## **5. SCLEROTHERAPY FOR VARICOSE VEINS**

### **TOPICS**

Sclerotherapy:

- indications

- contra-indications
- complications
- post-treatment compression

### **ANALYSED GUIDELINES**

- **USA 2011:** AVF/SVS guidelines.<sup>2</sup>
- **INDIA 2011:** Standard Guidelines for care: Sclerotherapy in dermatology. Indian Journal of Dermatology.<sup>166</sup>
- **UK 2013:** NICE guidelines.<sup>35</sup>
- **USA 2014:** Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders. American College of Phlebology (ACP), Society of Vascular Medicine (SVM), American Venous Forum (AVF), Society of Interventional Radiology (SIR).<sup>167</sup>
- **USA 2014:** Consensus for sclerotherapy. American Society for Dermatologic Surgery.<sup>168</sup>
- **EUROPE 2014:** European guidelines for sclerotherapy in chronic venous disorders.<sup>169</sup>
- **AUSTRALIA 2016:** Diagnose venous disease and treat superficial venous incompetence with injected sclerosants under ultrasound guidance 2016. ACP Standards Guidelines. Available in: <http://www.phlebology.com.au/standards>.<sup>170</sup>
- **AUSTRALIA 2016:** Assess and treat abnormal superficial venous network with injected sclerosants. 2016 ACP Standards Guidelines. Available in: <http://www.phlebology.com.au/standards>.<sup>171</sup>
- **LATIN AMERICA 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>

### **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

#### **1. Indications**

General agreement is reported in different continents guidelines regarding indication to sclerotherapy (Tab 5.1).

	INDIA 2011	USA AVF/SVS 2011	UK 2013	USA AVLS/AVF/SV M/SIR 2014	USA DERMATOL OGIC SURG 2014	EUROPE 2014	AUSTRA LIA 2016	LATAM 2016
<b>Saphenous v.</b>	x	TT over sclerothera py	If TT unavailable, foam sclerotherapy rather than surgery	x	x	1A	x	1B
<b>Tributary</b>	X	1B	X	x	x	1B	x	x
<b>Perforating v.</b>	x	2C	NOT FOUND	NOT FOUND	x	1B	x	2C
<b>Reticular v.</b>	x	1B	NOT FOUND	NOT FOUND	x	1A	x	1A
<b>Teleangectasia</b>	x	1B	NOT FOUND	NOT FOUND	x	1A	NOT FOUND	1A
<b>Recurrent v.</b>	x	2C	NOT FOUND	x	NOT FOUND	1B	x	x
<b>Pelvic v.</b>	NOT FOUND	2B	NOT FOUND	NOT FOUND	NOT FOUND	1B	x	1B
<b>Malformation</b>	therapy of choice in low flow	NOT FOUND	NOT FOUND	x	NOT F OUND	1B	x	NOT FOUND

**Tab. 5.1: Indication to sclerotherapy:**

A general agreement is found among the different guidelines on sclerotherapy indications, yet with different grade of evidence. The only major difference that can be noticed is between European<sup>169</sup> and Latin America<sup>8</sup> documents: despite Latin America<sup>8</sup> one is 2 years more recent, the indication to sclerotherapy for incompetent saphenous trunk was downgraded from 1A<sup>169</sup> to 1B<sup>8</sup> in these last one, while the indication to perforating vein treatment was downgraded from 1B<sup>169</sup> to 2C.<sup>8</sup>

Wherever marked with “X” the guidelines are indicating sclerotherapy treatment, but without a grade of evidence. Thermal Tumescence techniques (TT).

The only major difference that can be noticed is between European<sup>169</sup> and Latin America<sup>8</sup> documents: despite Latin America<sup>8</sup> one is 2 years more recent, the indication to sclerotherapy for incompetent saphenous trunk was downgraded from 1A<sup>169</sup> to 1B<sup>8</sup> in these last one, while the indication to perforating vein treatment was downgraded from 1B<sup>169</sup> to 2C.<sup>8</sup>

Another aspect of evident discrepancy among guidelines is represented by the maximum recommended sclerosant foam volume per session: 10 ml for the European guidelines<sup>169</sup> and 20 ml for the Australian ones.<sup>170</sup> Yet, the European guidelines allow volumes >10 ml according to the risk/benefit evaluation (grade 2C).<sup>169</sup> No other recommendations on the maximum volume were found in the other guidelines.

## **2. Contraindications**

Looking at the contraindications, a lack of uniformity can be identified in the different guidelines.

As reported in Table 5.2 (absolute contraindications) and Table 5.3 (relative contraindications) for example, Indian 2011<sup>166</sup> and the 2014 American Society for Dermatologic Surgery document<sup>168</sup> consider acute superficial thrombophlebitis as an absolute contraindication, while, always in 2014, the European consensus<sup>169</sup> considered it as relative, as the Australian ones did in 2016.<sup>170</sup>

The American Society for Dermatologic Surgery<sup>168</sup> is the only one enlisting leg edema and uncontrolled diabetes as relative contraindications. Regarding both diabetes and edema, Indian guidelines are simply mentioning that circulation is compromised in these conditions.<sup>166</sup> Australian guidelines are the only ones considering oral contraceptive, hormonal therapy, a recent trip >4 hours and a possible patient's lack of compliance as relative contraindications.<sup>171</sup> American 2014<sup>167</sup> and Latin America 2016<sup>8</sup> guidelines consider the asymptomatic right to left shunt as a relative contraindication, while the other analysed documents don't take this condition in consideration. The same 2014 American guidelines<sup>167</sup> are the only ones considering as relative contraindication a superficial vein thrombosis and, as absolute, a deep venous thrombosis/pulmonary embolism specifying their association with a previous sclerotherapy treatment. Indian guidelines<sup>166</sup> are the only ones considering pregnancy as absolute rather



than relative contraindication. Interestingly, the same guidelines<sup>166</sup> consider sapheno-femoral junction incompetence as relative contraindication.

<u>Absolute</u>	INDIA 2011	USA AVF/SVS 2011	UK 2013	USA AVLS/AVF/SV M/SIR 2014	USA DERMATO LOGIC SURG 2014	EUROPE 2014	AUSTRALIA 2016	LATAM 2016
ALLERGY TO SCLEROSANT	X	NOT FOUND	NOT FOUND	x	X	1C	x	X
ACUTE DVT/PE	x	NOT FOUND	NOT FOUND	Associated with previous sclerotherapy	x	1C	x	X
LOCAL/SEVERE GENERALIZED INFECTION	x	NOT FOUND	NOT FOUND	NOT FOUND	x	1C	NOT FOUND	NOT FOUND
LONG-LASTING IMMOBILITY	x	NOT FOUND	NOT FOUND	NOT FOUND	x	1C	NOT FOUND	NOT FOUND
KNOWN SYMPTOMATIC RIGHT TO LEFT SHUNT (for foam)	NOT FOUND	NOT FOUND	NOT FOUND	X	x	1C	Permanent neurological adverse event from previous sclerotherapy	NOT FOUND

**Tab. 5.2: Different absolute contraindications to sclerotherapy in international guidelines.**

Wherever marked with “X” the guidelines are indicating sclerotherapy treatment, but without a grade of evidence.

### 3. Complications

In the different guidelines, a general agreement is found in the description of the severe complications (Tab 5.4). To the contrary, more heterogeneity can be noticed in the description of the benign complications (Tab 5.5). NICE,<sup>40</sup> the American Society for Dermatologic Surgery<sup>168</sup> and the 2014

European Guidelines<sup>169</sup> are the only ones reporting the different complications incidence, yet with different values.

<b>RELATIVE</b>	<b>INDIA 2011</b>	<b>USA AVF/SVS 2011</b>	<b>UK 2013</b>	<b>USA AVLS/AV F/SVM/SIR 2014</b>	<b>USA DERMATO LOGIC SURG 2014</b>	<b>EUROPE 2014</b>	<b>AUSTRALIA 2016</b>	<b>LATAM 2016</b>
<b>PREGNANCY</b>	Absolute	Not Found	Not Found	Not Found	X	1C	X	Not Found
<b>BREAST FEEDING</b>		Not Found	Not Found	Not Found	Not Found	1C	X	Not Found
<b>SEVERE PERIPHERAL ARTERIAL DISEASE</b>	Absolute	Not Found	Not Found	Not Found	Absolute	1C	X	Not Found
<b>POOR GENERAL HEALTH</b>	Absolute	Not Found	Not Found	Not Found	X	1C	Not Found	Not Found
<b>STRONG PREDISPOSITION TO ALLERGY</b>	X	Not Found	Not Found	Not Found	X	1C	Not Found	Not Found
<b>HIGH THROMBO-EMBOLIC RISK</b>	X	Not Found	Not Found	Not Found	X	1C	X	Not Found
<b>ASYMPTOMATIC PATENT FORAMEN OVALE</b>	Not Found	Not Found	Not Found	X	Not Found	Not Found	Not Found	X
<b>UNCONTROLLED DIABETES</b>	Not Found	Not Found	Not Found	Not Found	X	Not Found	Not Found	Not Found
<b>LEG EDEMA</b>	Not Found	Not Found	Not Found	Not Found	X	Not Found	Not Found	Not Found
<b>ACUTE SUPERFICIAL THROMBOSIS</b>	Absolute	Not Found	Not Found	Associated With Previous Sclerotherapy	Absolute	1C	X	Not Found
<b>NEUROLOGICAL DISTURBANCES AFTER FOAM SCLEROTHERAPY</b>	Not Found	Not Found	Not Found	X	Not Found	1C	X	Not Found
<b>ORAL CONTRACEPTIVE/HORMONAL THERAPY</b>	Not Found	Not Found	Not Found	Not Found	Not Found	Not Found	X	Not Found
<b>POTENTIAL LACK OF COMPLIANCE</b>	Not Found	Not Found	Not Found	Not Found	Not Found	Not Found	X	Not Found
<b>RECENT &gt;4 HRS TRAVELS</b>	Not Found	Not Found	Not Found	Not Found	Not Found	Not Found	X	Not Found

**Tab. 5.3: Different relative contraindications to sclerotherapy in international guidelines.**

Wherever marked with “X” the guidelines are indicating sclerotherapy treatment, but without a grade of evidence.

<b><u>SEVERE COMPLICATIONS</u></b>	<b>INDIA 2011</b>	<b>USA AVF/SVS 2011</b>	<b>UK 2013</b>	<b>USA AVLS/AVF/SVM/SIR 2014</b>	<b>USA DERMATOLOGIC SURG 2014</b>	<b>EUROPE 2014 (GRADE 1B)</b>	<b>AUSTRALIA 2016</b>	<b>LATAM 2016</b>
<b>Anaphylaxis</b>	X	X	Not Found	Not Found	X	Isolated Cases	Not Found	X
<b>Large Tissue Necrosis</b>	X	X	Not Found	Not Found	X	Isolated Cases	Not Found	X
<b>Seizures</b>	Not Found	Not Found	1 Patient	Not Found	Not Found	Not Found	Not Found	Not Found
<b>Stroke/TIA</b>	Not Found	X	3 Patients (Patent Foramen Ovale)	Not Found	Not Found	Isolated Cases	Not Found	Not Found
<b>Myocardial Infarction</b>	Not Found	Not Found	1 Patient	Not Found	Not Found	Not Found	Not Found	Not Found
<b>Distal DVT</b>	X	X	Not Found	X	<1%	<1%	Not Found	X
<b>Proximal DVT</b>	X	X	Not Found	X	<1%	<0.01%	Not Found	X
<b>Pulmonary Embolism</b>	X	X	1/977	Not Found	<1%	Isolated Cases	Not Found	X
<b>Motor Nerve Injury</b>	X	X	Not Found	Not Found	X	Isolated Cases	Not Found	X

**Tab. 5.4: Severe complications and their incidence following sclerotherapy according to the different guidelines.** Wherever marked with “X” the guidelines are indicating sclerotherapy treatment, but without a grade of evidence.

<b>BENIGN COMPLICATIONS</b>	<b>INDIA 2011</b>	<b>USA AVF/SVS 2011</b>	<b>UK 2013</b>	<b>USA AVLS/AVF/SVM/SIR 2014</b>	<b>USA DERMATO LOGIC SURG 2014</b>	<b>EUROPE 2014 (GRADE 1B)</b>	<b>AUSTRALI A 2016</b>	<b>LATAM 2016</b>
<b>Visual disturbances</b>	X	X	5/977 Patients	X	0.09-2%	<1%	Not Found	X
<b>Headache</b>	Not Found	X	3/977	X	Not Found	<1%	Not Found	X
<b>Sensory nerve injury</b>	X	X	Not Found	Not Found	X	<0.01%	Not Found	X
<b>Chest tightness</b>	Not Found	Not Found	<3%	Not Found	Not Found	<0.01%	Not Found	Not Found
<b>Dry cough</b>	Not Found	Not Found	<3%	Not Found	Not Found	<0.01%	Not Found	X
<b>Superficial phlebitis</b>	X	X	7%	X	<1%	Unclear	Not Found	X
<b>Local allergy</b>	X	X	Not Found	Not Found	X	<0.01%	Not Found	X
<b>Matting</b>	X	X	Not Found	Not Found	15-24%	<10%	Not Found	X
<b>Pigmentation</b>	X	X	6%	X	X	<10%	Not Found	X
<b>Minimal skin necrosis</b>	X		Not Found	Not Found	X	<0.01%	Not Found	X

**Tab. 5.5: Benign complications and their incidence following sclerotherapy according to the different guidelines.** Wherever marked with “X” the guidelines are indicating sclerotherapy treatment, but without a grade of evidence.

#### 4. Post-sclerotherapy compression

Recommendations in post-procedural compression after sclerotherapy are reported in Table 5.6. The heterogeneity among international guidelines is extremely evident on this topic, not just in terms of pressure values, but also as for the grade of evidence, duration and even rationale.

In particular, the grade of evidence varies from the declared by NICE<sup>40</sup> lack of proper scientific data to the 1A grade of the Latin America guidelines.<sup>8</sup>

The pressure values range from 16 to 40 mmHg,<sup>2,166,167,170, 10</sup> while NICE,<sup>40</sup> European<sup>169</sup> and Latin America guidelines<sup>8</sup> are not reporting a specific pressure value.

The duration varies from 24 hrs to 3 weeks, with the 2019 AVF/SVS/AVLS<sup>82</sup> document indicating that, considering the lack of evidence on the topic, the choice is based on the best clinical judgment.

The same rationale for compression changes among the documents, including anti-inflammation, vein size reduction, bruising and pigmentation control and a better aesthetic outcome.

	INDIA 2011	USA AVF/SVS 2011	UK 2013	USA AVLS/AVF/SVM /SIR 2014	USA DERMATOL OGIC SURG 2014	EUROPE 2014	AUSTR ALIA 2016	LATAM 2016	USA 2019 AVF/SVS/A VLS
<b>GRADE OF EVIDENCE</b>	Not Reported	Not Reported	Not Reported	Declared Unknown Benefit	Not Reported	2b	Not Reported	1a	2c
<b>mmHg</b>	Smaller Veins: 16 mmHg Larger Veins: 20-30 mmHg	Liquid (Aesthetic): 30-40 mmHg Foam: 30-40 mmHg Stockings And/Or Bandage	Bandages Or Graduated Compression Stockings: Undefined Pressure Level	Bandages Or Graduated Compression Stockings: Undefined Pressure Level	Teleangiectasia: 15-20 mmHg Reticular: 20-30 mmHg Small Varices: 20-30 mmHg Truncal: 30 To 40 mmHg	23-32 mmHg	Class 2 (Unspecified mmHg)	Not Reported	Not Reported
<b>DURATION</b>	2 Weeks (Up To 3 Weeks Based On The Vessel Calibre). Declared Lack Of Consensus	Liquid (Aesthetic) 1-3 Days Liquid (Treatment) : At Least 1 Week Foam: 1 Or 2 Weeks	1 Week – 1 Month	Not Reported	24-48 Hrs	3 Weeks	Not Reported	Not Reported	Best Clinical Judgment

		(Eventually Less Than 1 Week)							
<b>REASON FOR COMPRESSION</b>	Not Reported	Not Reported	Anti-Inflammatory	Not Reported	Wall Apposition	Aesthetic Improvement	Not Reported	Not Reported	Wall Apposition, Reduction Of Bruising And Pigmentation

**Tab. 5.6: Post-sclerotherapy compression recommendations according to different guidelines.**

The grade of evidence varies from the declared by NICE<sup>40</sup> lack of proper scientific data to the 1A grade of the Latin America guidelines.<sup>8</sup> The pressure values range from 16 to 40 mmHg,<sup>2,166,167,170,10</sup> while NICE,<sup>40</sup> European<sup>169</sup> and Latin America guidelines<sup>8</sup> are not specifying a specific pressure value.

The duration varies from 24 hrs to 3 weeks, with the 2019 AVF/SVS/AVLS<sup>82</sup> document indicating that, considering the lack of evidence on the topic, the choice is based on the best clinical judgment.

### **SIGNIFICANT NEW DATA REPORTED AT THE MEETING**

In 2016 a revision of the literature evaluated controlled trials comparing endothermal ablations with ultrasound guided foam sclerotherapy for truncal ablation. Despite the higher anatomical success of endothermal ablations, no significant differences were reported between the two techniques in terms of patient reported outcomes and clinical success, with a better cost-effectiveness for sclerotherapy, so questioning the current indications favouring endothermal approaches for truncal ablation.<sup>172</sup>

Yet in 2018 these data were questioned by another revision, pointing out the significantly higher need of re-treatment in patients undergoing truncal sclerotherapy versus thermal-ablation.<sup>173</sup>

These anatomical data at the great saphenous vein are confirmed by the 5 years analysis of Rasmussen, but it's interesting to point out that the clinical recurrence didn't overlap the occlusion rate of the different techniques, thus keeping the discussion open.<sup>174</sup>

An 8-years randomized comparative trial published in 2018 showed that stripping compared to sclerotherapy of the GSV led to a better anatomical success and less symptoms recurrence, yet with no significant differences at the EQ-5D standardized measure of health status.<sup>175</sup>

On this topic, in 2019 Kalodiki et al published a discord outcome analysis comparing endovenous laser ablation and foam sclerotherapy for GSV reflux treatment, including evaluation of change in Aberdeen Varicose Veins Questionnaire (AVVQ), Venous Clinical Severity Score (VCSS) and Venous Filling Index (VFI). Interestingly, at 68 months, no significant differences in VCSS and VFI were found, while the laser group had an improvement in AVVQ. This investigation raises again concerns on the current way of evaluating procedural success following superficial venous reflux treatment.<sup>176</sup>

A fundamental bias to be taken into consideration in all these analysis is the foam performance variability depending on the same production method and on the different materials. Unfortunately, the vast majority of the available investigations is not reporting the specifics of the material and method used in foam production.

Recent data demonstrated the significant impact on foam half-life of the surfactant, temperature, injection velocity and syringe size, in decreasing order of effect intensity.<sup>177</sup>

In 2019, data showed that adding drugs such as sulodexide to polidocanol or sodium tetradecyl sulfate can even lead to a foam half-life prolongation.<sup>178</sup> A potential step-forward in foam sclerotherapy homogeneity has been offered by the non physician-compounded polidocanol endovenous microfoam (Varithena®), whose efficacy and safety resulted to be equivalent or even better than physician-compounded foam. Nevertheless, the comparison was done just against placebo and with only 1% concentration.<sup>179</sup>

On the other side, recent literature has pointed out the versatility of sclerotherapy as hybrid technique in venous disease treatment. In 2018 Kolluri described the potential technical benefit of injecting foam sclerotherapy before an ultrasound guided phlebectomy.<sup>180</sup>

In the last 10 years a few publications reported about a higher saphenous occlusion rate following foam sclerotherapy by means of a long catheter. Furthermore, the combination of catheter foam sclerotherapy with ultrasound-guided peri-saphenous tumescence infiltration and vein irrigation, prior to foam delivery, resulted in an up to 96.5% reflux-free rate at 3 years follow-up in two prospective studies published in 2017.<sup>181,182</sup>

In 2019 the utility of performing an intra-operative sapheno-popliteal junction sclerosis right before a surgical ligation was published. Small saphenous vein reflux treatment remains an area lacking strong evidence concerning the best treatment selection and sclerotherapy results to be a potential aid in this anatomical scenario.<sup>183</sup>

Always in 2019, the possibility of using sclerotherapy in a hybrid surgical technique was reported for venous malformations treatment.<sup>184</sup>

## **DISCUSSION**

Starting from its dawn in the mid 19<sup>th</sup> century,<sup>185</sup> sclerotherapy has progressively dominated all the offices dedicated to varicose veins treatment. Its safety profile is nowadays well proven, so fostering an even greater and more aware use.<sup>186-188</sup>

Despite evidence of correlation between a patent foramen ovale and possible neurological adverse events,<sup>189</sup> the safety profile is so high that international guidelines are not recommending standard screening for right-to-left shunts.<sup>169</sup>

Both safety and efficacy evaluation require a proper standardization of the materials and methods used. In fact, the current literature is biased not only by the lack of specifics regarding the used syringes and related foam production methods, but also regarding the number of injections per treatment. Sclerotherapy safety is associated indeed with the neutralizing power of the same blood toward the drug.<sup>190</sup> At the same time, this phenomenon leads to the possible impact of the sclerosant dilution inside the blood stream: the same amount of sclerosant can be introduced in the blood stream by different numbers of injections, so leading to possible different grades of inactivation.

Guidelines are not reporting specifics on this topic, with the exception of the Latin America ones<sup>8</sup> that are actually giving some indications regarding the needle size and the injection methodology. Guidelines are also not reporting specifics regarding the gas used to produce foam sclerotherapy.



In a 2010 retrospective comparison, CO<sub>2</sub>/O<sub>2</sub> gas mixture resulted to be associated with less chest tightness, dry cough and dizziness.<sup>191</sup> In 2012, no differences were found in efficacy or side-effects between room-air and CO<sub>2</sub> foam.<sup>192</sup>

In 2015 a review suggested a higher safety profile of foam sclerotherapy performed using biocompatible gases rather than room air. Yet significant heterogeneity among the different studies methodology was found, introducing the risk of significant bias.<sup>193</sup>

Future investigation should properly randomized different gasses in a properly calculated statistical analysis, looking for eventually significant differences in terms of safety and efficacy. Endothelial catabolites release following sclerotherapy has been recently considered potentially involved in eventual complication pathogenesis.<sup>194</sup>

Yet no clear cause-effect mechanism has been already proved and the advent of new techniques combining foam with a massive mechanical endothelial stress, such as the mechano-chemical ablation, haven't reported significantly higher complications rate and/or correlation with increased levels of endothelial byproducts.<sup>195</sup>

The same mechano-chemical ablation technique has recently demonstrated the importance of a proper penetration of the sclerosant agent inside the vein wall, reaching the media layer, rather than just the endothelial lining.<sup>196</sup>

This data lead to the consideration of the wall thickness heterogeneity as another potential bias in current sclerotherapy performance evaluation.

In conclusion, even the simple practical data of the enormous number of sclerotherapy acts performed worldwide daily in absence of significant complications testifies the safety profile of this therapeutic option. Yet, proper standardization in the materials and methods is mandatory for proper efficacy and cost-effectiveness analysis.

Future international guidelines should focus on the evaluation of homogeneous data, discarding investigations potentially affected by significant biases, so providing evidence-based support to what empirically has been the most frequently used practice in the phlebology offices all around the world.

## **KEY MESSAGES**

- Maximum amount of sclerosant volume per session is variable among countries.
- Post-sclerotherapy compression is generally recommended in the different guidelines, but with significant heterogeneity in the grade of evidence, dose and duration.
- Sclerotherapy is considered universally safe. Some differences can be noted among international guidelines list of possible complications, absolute and relative contraindications.
- Compounded-foam sclerotherapy can be standardized and reproducible in its production, but requires standardized methodology and materials.
- Hybrid procedures involving foam and eventual use of catheters are showing potential expansion in future use.
- Sclerosant agent inactivation by blood makes the report of the number of injections per treated vein segment fundamental in order to analyse homogeneous data in sclerotherapy performance.

## **SUGGESTED RESEARCH TOPICS**

- Discord outcome analysis or comparison among the different techniques for chronic venous disease treatment.
- Sclerotherapy cost-effective analysis based on patient reported outcomes and not only on anatomical vessel ablation.
- Comparison among foam sclerotherapy and hybrid procedures involving sclerotherapy.
- Real need of biocompatible gas for foam production versus room air.
- All future investigations on sclerotherapy should adopt standardized and reproducible methods in foam sclerotherapy production and injection.

## **6. AESTHETIC PHLEBOLOGY**

### **TOPICS**

- Aesthetic sclerotherapy

- Aesthetic laser

### **ANALYSED GUIDELINES**

- **USA 2011:** American Venous Forum (AVF)/ Society of Vascular Surgery (SVS) guidelines.<sup>2</sup>
- **EUROPE 2014:** European guidelines for sclerotherapy in chronic venous disorders.<sup>160</sup>
- **EUROPE 2015:** European Society for Laser Dermatology guidelines of care for vascular lasers and intense pulse light sources.<sup>197</sup>
- **EUROPE 2015:** Guidelines of the European Society for Vascular Surgery (ESVS).<sup>6</sup>
- **LATIN AMERICA 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>

### **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

A paucity of international guidelines has been found dealing with indications for aesthetic treatment of the lower limb veins, despite the high incidence of this complaint and related sclerotherapy/laser approach worldwide.<sup>2,6,8,169,197</sup>

A general agreement among guidelines exists in the need of proper history and ultrasound scanning analysis before approaching a treatment for chronic venous disease. At the same time, disagreement on the grade of recommendation can be found between AVF/SVS guidelines (grade 1 A)<sup>2</sup> and the European Society for Laser Dermatology ones (grade 1 C).<sup>197</sup> No specific recommendation is expressed in the aesthetic case scenario and no indications are reported regarding how specific findings could alter the therapeutic/aesthetic approach (Tab 6.1).

AVF/SVS 2011 guidelines<sup>2</sup> are the only ones suggesting the use of loupes and transillumination for helping sclerotherapy injection, but without a specific grade of evidence.

	USA AVF/SVS 2011	EUROPE European guidelines for sclerotherapy in chronic venous disorders 2014	EUROPE European Society for Laser Dermatology 2015	LATAM 2016
<b>HISTORY</b>	1A (not specific for C1)	Not graded (not specific for C1)	1C In case of signs of chronic venous disorder other than leg telangiectasia, especially with C2	Not graded (not specific for C1)
<b>ULTRASOUND SCANNING</b>	1A (not specific for C1)	1C CW-Doppler can be enough	1C In case of signs of chronic venous disorder other than leg telangiectasia, especially with C2	Not graded (not specific for C1)

**Tab. 6.1: Different guidelines recommendations for assessment before aesthetic procedures on lower limb spider veins.** AVF/SVS 2011 guidelines<sup>2</sup> are the only ones suggesting the use of loupes and transillumination for helping sclerotherapy injection, but without a specific grade of evidence.

### 1. Aesthetic sclerotherapy

European,<sup>169</sup> Latin America<sup>8</sup> and AVF/SVS<sup>2</sup> guidelines are indicating 27-32 g needles for reticular and teleangiectasia treatment. AVF/SVS<sup>2</sup> and European<sup>169</sup> guidelines are basically overlapping in the suggested concentrations, while Latin America<sup>8</sup> guidelines suggest not to use less than 0.5% POL as it could be ineffective. Liquid form is recommended in all the analysed guidelines with the European documents<sup>6,169</sup> reporting foam as a possible alternative (grade 2B), as done by the Latin America guidelines,<sup>8</sup> yet with a different grade of evidence (grade 1A). The grade of evidence of the recommendation for liquid sclerotherapy differs between the different guidelines inside the same Europe, with the 2014<sup>169</sup> document reporting a grade 1A versus the 1B grade of the ESVS paper.<sup>6</sup>

The maximum sclerosant volume per injection is around 1 cc for both AVF/SVS<sup>2</sup> and Latin America guidelines,<sup>8</sup> while for the European 2014 guidelines it ranges between 0.2 to 0.5 cc.<sup>169</sup> The other analysed documents are not specifying the amount. Latin America guidelines<sup>8</sup> are the only ones recommending a post-treatment visit specific time of 2-3 weeks and, as the AVF/SVS 2011,<sup>2</sup> they are also encouraging photo-documentation, even if not with a specific grade of evidence. Photo documentation is recommended with a grade 1C by the European Society for Laser Dermatology.<sup>197</sup> At

the follow-up visit, eventual clot removal is mentioned only by the 2014 European guidelines (grade 1C)<sup>169</sup> and by the Latin America document (no specific grade).<sup>8</sup> Post-sclerotherapy compression is indicated in all the guidelines, yet with different pressure values and with a timing ranging from 8 hours to 4 weeks.<sup>2,6,8,169</sup> Only the European documents specify a grade of evidence on this topic, with the 2014<sup>169</sup> indications being specifically addressed to aesthetic sclerotherapy and with the 2015<sup>6</sup> paper covering in general chronic venous disease (Tab 6.2).

	<b>USA AVF/SVS 2011</b>	<b>EUROPE European guidelines for sclerotherapy in chronic venous disorders 2014</b>	<b>EUROPE ESVS 2015</b>	<b>LATAM 2016</b>
<b>DRUG &amp; CONCENTRATION</b>	(NO GRADE) <b>TELEANGECTASIA</b> STS 0.125 -0.25% POL 0.25% - 0.6% <b>RETICULAR VEINS</b> STS 0.25 -0.5% POL 0.6% - 1% Maximum 1 ml per injection (not more than 10-20 injections)	<b>2B TELEANGECTASIA</b> STS 0.1 -0.2% POL 0.25% - 0.5% <b>RETICULAR VEINS</b> STS up to 0.5% POL 0.5 – 1% Maximum 0.2 ml (teleangectasia)and 0.5 ml (reticular v.) per injection	<b>IaB</b> for teleangectasia and reticular v.  <b>IbC</b> Transcutaneous laser may be indicated for teleangectasia only when sclerotherapy is not feasible	(NO GRADE) <b>TELEANGECTASIA &amp; RETICULAR</b> POL 0,5% Maximum 1-1,5 cc per injection
<b>LIQUID /FOAM</b>	(NO GRADE) <b>LIQUID</b>	<b>1A LIQUID</b> Foam is an alternative method (2B)	<b>IaB LIQUID</b>	<b>TELEANGECTASIA: LIQUID (1A) RETICULAR: LIQUID or FOAM (1 A)</b>
<b>SESSION TIMING</b>	NOT REPORTED	NOT REPORTED	NOT REPORTED	2-3 weeks
<b>PICTURE DOCUMENTATION</b>	(NO GRADE) encouraged	NOT REPORTED	NOT REPORTED	(NO GRADE) encouraged

<b>COMPRESSION</b>	Gauze pads + 30-40 mmHg 1 to 3 days (NO GRADE)	2B 23-32 mmHg 3 weeks	1B to control chronic venous disease signs	(NO GRADE) From 8 to 24 hrs
<b>CLOT REMOVAL</b>	NOT REPORTED	1C When feasible at the follow up visit (not specified timing)	NOT REPORTED	Before 2 weeks

**Tab. 6.2: International guidelines recommendations for aesthetic sclerotherapy.** Significant heterogeneity is evident among different guidelines.

## 2. Aesthetic lasers

ESVS 2015 guidelines<sup>6</sup> state that transdermal laser may be indicated for treatment of teleangiectasias only when sclerotherapy is not applicable (grade IIBc). The 2015 European Society for Laser Dermatology<sup>197</sup> confirmed that sclerotherapy is the first-line treatment for leg veins aesthetic management, leaving room for transcutaneous laser approaches in case of needle-phobia, allergy to the sclerosants and previous sclerotherapy side effects. Latin America document<sup>8</sup> reports specific indications for laser treatment, yet with different grades of evidence and slight different vessel calibre indications compared to the analogous European document<sup>6</sup> (Tab 6.3). No specific guidelines on the topic were found from the North American societies.

Some recommendations without grade of evidence can be found in dedicated papers, pointing out the importance of proper parameters setting, such as target chromophore, penetration depth, pulse duration, radiant exposure, spot size. In general, the choice of the appropriate laser type is mainly based on the vessel calibre, with <600 nm for <1 mm vessels, and Nd:YAG for larger vessels.

Nd:YAG is considered the best choice in case of dark skin types because of the low absorption by melanin. At the same time, high pain scores have not been reported with this device.<sup>198</sup>

<p style="text-align: center;"><b>EUROPE</b> European Society for Laser Dermatology 2015</p>	<p style="text-align: center;"><b>LATAM</b> 2016</p>
<p style="text-align: center;"><b>1A</b> Nd:YAG for vein&gt;1mm</p>	<p style="text-align: center;"><b>1C</b> Nd:YAG for vein&lt;3mm</p>
<p style="text-align: center;"><b>1C</b> As second option for &gt;1mm 755, 800, 810, 940, 983 nm</p>	<p style="text-align: center;"><b>2C</b> 820-980 nm for reticular v.</p>
<p style="text-align: center;"><b>1A</b> 532-595 nm &lt; 1mm vessels</p>	<p style="text-align: center;"><b>1C</b> Intense pulsed light, 550-532 nm, NdYag Vein&lt;0.5 mm, matting</p>
<p><b>Skin cooling</b> 1B</p>	<p><b>Skin cooling</b> 1C</p>
	<p><b>1B</b> Nd:YAG + liquid sclerotherapy (Crio Laser - Crio Sclerotherapy) (not specified for which calibre)</p>

**Tab. 6.3: European and Latin America guidelines in laser treatment of reticular veins and telangiectasia.** Significant differences in the evidence grade is evident.

Multiple wave-length intense pulsed lasers can be considered,<sup>199</sup> but controlled clinical trials are lacking and a strong supporting data are missing, so making it not a first-choice option.

McCoppin stressed the importance of a careful observation of the skin reaction after deliverance of a test pulse before treating the entire lesion, so to adjust the parameters setting on the specific skin type.<sup>200</sup>

In 2003 Saddick proposed a series of recommendation for Nd:YAG laser treatment of leg spider veins, indicating spot sizes from 1.5 to 3 mm, radiant exposure from 200 to 600 J/cm<sup>2</sup>, pulse widths from 30 to 60 ms.<sup>201</sup>

In the same year Mordon reported the possibility of using multiwave lengths emission to transform the heme in methemoglobin, which is up to 4 times more absorbed than the other blood constituents. A combination of 595 nm from a pulsed dye laser followed by 1064 nm Nd:YAG emission demonstrated to allow lower treatment Nd:YAG fluences.<sup>202</sup>

### **SIGNIFICANT RECENT DATA RELATED TO THE MEETING DISCUSSION**

In 2017 JAMA reported the possibility of obtaining a better effect than 75% hypertonic glucose alone by adding 70% hypertonic glucose to 0.2% polidocanol, with no difference in complication rates.<sup>203</sup>

Always in 2017 it was demonstrated that Sodium tetradecyl sulfate 0.15% and polidocanol 0.31% are the best concentrations for 0.8 mm to 1 mm leg telangiectasia, both according to the histological and clinical evaluation. Sodium tetradecyl sulfate foam is comparable to polidocanol foam at these concentrations as well.<sup>204</sup>

In 2018, 27 possible risk factors for matting were analysed, finding out that statistically significant ones were epistaxis, easy bruising, hypersensitivity (eczema, hives, hay fever, and rhinitis), previous treatment with sclerotherapy or endovenous laser for lower limb veins, and a family history of telangiectasias. Oral contraceptives, hormone replacement therapy, haemostatic alterations and age were not associated with an increased matting incidence. A mast-cell hyperactivity together with a bleeding tendency have been hypothesized as predisposing factors.<sup>205</sup>

In 2019, 5 years follow up data showed the satisfying results of a technique injecting foam sclerotherapy (polidocanol) immediately followed by Nd:YAG long-pulse emission.<sup>206</sup>

In the same year, a randomized comparative study assessing hypertonic saline, polidocanol and Nd:Yag concluded that sclerotherapy remains the gold standard in vessels > 1mm, while Nd:YAG can have a role in smaller vessels.<sup>207</sup> Always in 2019, the feasibility of combining 532 and 808 nm multi-wavelength emissions for <1 mm vessels was demonstrated.<sup>208</sup>



## **DISCUSSION**

Leg telangiectasias and reticular veins are a cosmetic complaint affecting up to 80% of the population, whose treatment is an extremely diffused practice worldwide.<sup>209</sup> Yet, international guidelines are lacking in clear evidence-based recommendations. A pre-treatment ultrasound scanning is fundamental considering that 26% of patients with teleangiectasia have truncal varices vs 14% of subjects without spider veins.<sup>209</sup> The general idea is that chronic venous disease refluxes must be treated before the aesthetic component, so to avoid venous hypertension potentially triggering recurrences. To the best of our knowledge, limited evidence based data<sup>210,211</sup> are available on this topic and future investigations should clarify this common belief, even if rightfully based on the concept that the treatment of a pathological aspect should always precede the aesthetic issue. Moreover, future research lines should try to make the different telangiectasias classifications more homogeneous, incorporating both morphological (spider, arboriform, filiform, point-like, etc) and colorimetric features (bright red, light red, blue, mixed).<sup>212,213</sup>

Of paramount importance will be also the investigations aimed to establish the relationship that links spider veins to the deeper systems.<sup>214-222</sup>

Indeed, the same strategy treatment for spider veins must follow the specific reflux pattern assessment, exactly as it is for varices management.

Unfortunately, even more than in venous insufficiency, homogeneous data are lacking in this field compromising a correct evaluation in the comparative studies between the different techniques/methods.

In 2006 a Cochrane revision of the literature reported no significant differences in aesthetic sclerotherapy with different sclerosants, dosages, formulations, local pressure dressings, degrees and length of compression.<sup>223</sup> Nd:YAG laser has been the most extensively investigated laser in leg aesthetic vein treatment, because of its ability to treat also >1 mm vessels at >1 mm depth.

A direct comparison with sclerotherapy showed better vessel clearance following this last technique.<sup>224</sup>

Residual pigmentation and matting incidence doesn't show significant differences between the two treatment modalities.<sup>225-227</sup> It should be noted that, up to our knowledge, no longer than 3 months follow

up investigations are reported in the comparison between laser and sclerotherapy, so that making final statements of superiority between the two techniques is not possible.<sup>228</sup> In the same way, comparison data are missing regarding the potential combination of sclerotherapy followed by Nd:YAG treatment: an option that has been proposed already more than 15 years ago.<sup>229</sup> To the contrary, data show no benefit in combining pulsed dye laser with sclerotherapy.<sup>230</sup> Innovative devices combining diode laser and radiofrequency emission have been reported in the literature, yet without a direct comparison with laser only treatment.<sup>231,232</sup> A recent technical variant includes the injection of indocyanin green before the alexandrite laser treatment, to maximize the absorption at 700-801 nm, so maximizing the laser selective effect.<sup>233</sup> In a recent study by Klein, this treatment choice demonstrated to be more effective than pulsed dye laser and diode laser ones.<sup>234</sup> The superiority of indocyanin green was reported also versus Nd:YAG, even if associated with higher pain scores.<sup>235</sup> Empirically, radiofrequency diathermy is sometimes used to treat teleangiectasia and residual veins. The panel was not able to find guidelines and document providing evidence-based recommendations on its use. A new tendency in aesthetic phlebology is the hands vein treatment. A limited literature is available, showing the feasibility of the procedure. Nevertheless, well designed investigations are needed before formulating proper evidence-based indications.<sup>236</sup> Sclerotherapy is considered the gold standard in most cases because of the possibility of treating in a satisfying and cost-effective way the vast majority of vessels, particularly injecting the feeding vein rather than the whole vascular area, so reducing the pain and the side effects occurrence. Yet no homogeneous evidence based data are available for the comparison between sclerotherapy and laser techniques, which currently result to be more complimentary and eventually synergistic rather than competitive. Future research lines should carefully include detailed descriptions of the materials and methods used in the sclerotherapy act. At the same time, the same investigations should specify the laser settings and the used protocols, currently at the discretion of the single treating physicians. This aspect represents a significant bias of the analysed data, so making final conclusions and recommendations on the topic not significant at the moment. An example of this can be found in the observation that the spatial extent of photocoagulation has a significant impact on the long-term removal

of coagulated vessels, leading to a possible reperfusion if a too short segment is treated.<sup>237</sup>

The phenomenon stress out the importance of homogeneity in the technique in order to produce valuable clinical results, suitable for proper comparison among different laser approaches evidence-based comparison. In conclusion, in order to properly report evidence-based data and clinical recommendations related to aesthetic phlebology, future investigations should focus on identify proper objective assessment tools for proper homogeneous comparison. This aspect includes photographic material (itself a potential bias in patient satisfaction analysis according to recent literature),<sup>238</sup> quantification of the aesthetic lesion and the impact on patient satisfaction score. The same patient subjectivity and self-perception should be taken into consideration as possible confounding factor.

A need to move from empiricism to evidence-based science is extremely present in aesthetic phlebology.

### **KEY MESSAGES**

- International guidelines agree on the need of proper ultrasound evaluation before aesthetic vein treatment. The grade of evidence for this recommendation change in the different guidelines.
- Only AVF/SVS guidelines recommend loupes and transillumination for spider veins treatment.
- Guidelines are agreeing in considering sclerotherapy as first line treatment for spider veins, reserving laser ablation to the cases in which sclerotherapy is not feasible.
- Multi-wave lengths emission is showing promising outcomes in spider veins treatment.
- No longer than 3 months follow up investigations are reported in the comparison between laser and sclerotherapy, so that making final statements of superiority between the two techniques is not possible.
- Residual pigmentation and matting remain a not rare complication of venous aesthetic procedures.
- Graduated compression is recommended in the different international guidelines after aesthetic treatment, but with different doses and grade of evidence.
- Evidence-based data indications on hands vein treatment are missing.

## **SUGGESTED RESEARCH TOPICS**

- Performance of combined laser and sclerotherapy approach in spider veins treatment.
- Homogeneous comparison among different setting parameters in aesthetic vein laser treatment.
- Assessment of best combination in multi-wave lengths laser emission for aesthetic vein treatment.
- Modalities to reduce post-aesthetic treatment hyperpigmentation.
- Homogeneous randomized comparative trials on post-aesthetic treatment leg graduated compression.

## **7. ACUTE AND CHRONIC DEEP VEIN DISEASE**

### **TOPICS**

- Acute deep vein disease interventional treatment
- Chronic deep vein disease interventional treatment

### **ANALYSED GUIDELINES**

- **USA 2012:** Early thrombus removal strategies for acute deep vein thrombosis: clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF).<sup>239</sup>
- **UK 2012:** NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing.<sup>240</sup>
- **GLOBAL 2013:** Cardiovascular Disease Educational and Research Trust, European Venous Forum (EVF), North American Thrombosis Forum, International Union of Angiology (IUA) and Union Internationale du Phlebologie (UIP).<sup>241</sup>
- **EUROPE 2014:** Society of Interventional Radiology (SIR) and Cardiovascular and Interventional Radiological Society (CIRS).<sup>242</sup>
- **USA 2014:** Management of venous leg ulcers: clinical practice guidelines of the SVS and AVF.<sup>32</sup>
- **USA 2014:** American Heart Association (AHA) guidelines.<sup>243</sup>

- **EUROPE 2015:** Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS).<sup>6</sup>
- **USA 2015:** Management of Obstruction of the Femoro-iliocaval Venous System. American Vein and Lymphatic Society (AVLS, former American College of Phlebology).<sup>244</sup>
- **UK 2015:** NICE guidelines. Ultrasound enhanced, catheter directed thrombolysis for deep vein thrombosis.<sup>245</sup>
- **USA 2016:** CHEST guidelines.<sup>122</sup>
- **LATIN AMERICA 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>
- **EUROPE 2018:** European Society of Cardiology (ESC).<sup>246</sup>

## **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

Topics related to diagnostics and compression for lower limb deep venous pathology have been already covered in the dedicated sessions of this document. This part is dedicated to the interventional options.

### **1. Acute deep venous interventional treatment**

International indications for early thrombus removal in lower limb acute deep venous thrombosis are given with a low level of evidence and with a noticeable heterogeneity (Tab 7.1). Among the analysed documents, only SVS/AVF<sup>239</sup> and CHEST<sup>122</sup> report a grade of evidence. The AVF/SVS document<sup>217</sup> recommends pharmaco-mechanical thrombectomy over catheter directed pharmacologic thrombolysis alone, while CHEST<sup>122</sup> recommends anticoagulant therapy alone versus catheter directed thrombolysis. The 2013 EVF/IUA/UIP document recommends catheter-directed thrombolysis or pharmaco-mechanical thrombolysis, in selected patients with iliofemoral DVT treated in expert centers, while recognizing there is low level of evidence.<sup>241</sup> In 2014, the European SIR guidelines also recommended endovascular thrombus removal, but with a different eligibility treatment period of symptoms onset <28 days rather than the usually considered 14 days.<sup>233</sup> In 2015, NICE guidelines recommended catheter-directed thrombolysis, while percutaneous mechanical thrombectomy is still under evaluation.<sup>245</sup> The most recent document from the European Society of Cardiology supports the eventual use of catheter-

directed thrombolysis, while recommends against the primary use of mechanical thrombus removal alone.<sup>246</sup> In June 2019 NICE is expected to release recommendations regarding percutaneous mechanical thrombectomy for acute deep vein thrombosis of the leg.<sup>247</sup>

USA AVF/SVS 2012	EUROPE EVF, UIP, IUA 2013	EUROPE SIR 2014	UK NICE 2015	USA CHEST 2016	EUROPE European Society of Cardiology 2018
<p><b>2C</b> early thrombus removal strategies in ambulatory patients with: good functional capacity a first episode of ilio-femoral DVT &lt;14 days</p> <p><b>1A</b> strongly recommend their use in patients with limb-threatening ischemia due to ilio-femoral venous outflow obstruction</p> <p><b>2C</b> <b>PHARMACO-MECHANICAL</b> strategies over catheter-directed pharmacologic thrombolysis alone surgical thrombectomy if thrombolytic therapy is contraindicated</p>	<p><b>LOW LEVEL OF EVIDENCE</b> early thrombus removal using <b>CATHETER-DIRECTED THROMBOLYSIS</b> (level of evidence: low) or <b>PHARMACO-MECHANICAL THROMBOLYSIS</b> (level of evidence: low) may be used in expert centers in selected patients with iliofemoral DVT. If thrombolysis is contraindicated, surgical thrombectomy could be used in expert centers.</p>	<p><b>NOT GRADED ENDOVASCULAR THROMBUS REMOVAL</b> Imaging-proven symptomatic DVT in IVC or iliac, common femoral, and/or femoral vein in a recently ambulatory patient with DVT symptoms for o 28 d or in whom there is strong clinical suspicion for recently formed (o 28 d) DVT</p>	<p><b>NOT GRADED</b> Early thrombus removal (<b>CATHETER-DIRECTED THROMBOLYSIS</b>) for ambulatory patients with:</p> <ul style="list-style-type: none"> <li>• &lt;14 days symptoms</li> <li>• Good functional status</li> <li>• Life expectancy &gt;1 y</li> <li>• Low risk of bleeding</li> </ul> <p><b>PERCUTANEOUS MECHANICAL THROMBECTOMY</b> is under evaluation</p>	<p><b>2C</b> In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over <b>CATHETER-DIRECTED THROMBOLYSIS</b></p>	<p><b>NOT GRADED</b> Adjuvant <b>CATHETER-DIRECTED THROMBOLYSIS</b> may be considered in selected patients with ilio- common femoral DVT, symptoms &lt;14 days, and life expectancy &gt;1 year if performed in experienced centres. Primary acute DVT stenting or <b>MECHANICAL</b> thrombus removal alone are not recommended..</p>

**Tab. 7.1: Different indications for early thrombus removal in international guidelines.** Only SVS/AVF<sup>239</sup> and CHEST<sup>122</sup> report a grade of evidence.

## 2. Chronic deep venous interventional treatment

European, North and South American guidelines are agreeing in indicating percutaneous transluminal angioplasty (PTA) and stenting for severely symptomatic patients, with only the AHA<sup>243</sup> and ESVS<sup>6</sup> documents still taking into consideration a surgical approach, even if with a low level of evidence (Tab

7.2). A significant increase in the recommendation strength can be noticed in the AVLS<sup>244</sup> and Latin America<sup>8</sup> documents, yet randomized controlled trials are still missing.

	USA AVF/SVS 2014	USA AHA 2014	EUROPE ESVS 2015	USA AVLS 2015	LATAM 2016
<b>Patients without ulcer</b>					
<b>PTA + stent</b>		<b>IIBB</b> Severly symptomatic	<b>IIBB</b> Symptomatic patients	<b>1B</b> (ilio-femoral) <b>1C</b> (inferior vena cava) Leg pain/edema affecting QOL not palliated by compression	<b>1A</b> to improve symptoms and quality of life
<b>Single PTA</b>			<b>IIIAc</b> Symptomatic patients NOT as single treatment		
<b>Open surgery</b>		<b>IIBc</b> Severely symptomatic	<b>IIIC</b> Not recommended as primary treatment		
<b>Patients with ulcer</b>					
<b>PTA + stent</b>	<b>1C</b>			<b>1B</b> Iliofemoral <b>1C</b> Inferior vena cava	<b>1A</b> to improve symptoms and quality of life
<b>Single PTA</b>					
<b>Open surgery</b>	<b>2C</b> if endovascular treatment failed				

**Tab. 7.2: International recommendations on percutaneous transluminal angioplasty (PTA) and stenting for lower limb chronic deep venous disease.** European, North and South American guidelines are agreeing in indicating percutaneous transluminal angioplasty (PTA) and stenting for severely symptomatic patients, with only the AHA<sup>243</sup> and ESVS<sup>6</sup> documents still taking into consideration a surgical approach, even if with a low level of evidence.

## **SIGNIFICANT NEW DATA RELATED TO THE MEETING DISCUSSION**

### **1. Acute deep venous interventional treatment**

In 2016 the 5 years follow up outcomes of the CAVENT study were published showing a significant improvement of the ilio-femoral patency and a significant reduction in post-thrombotic syndrome (PTS)

incidence following catheter-directed thrombolysis (CDT) versus anticoagulation alone. While an absolute risk reduction of 28% in developing PTS was seen in the thrombolysis group, there was no significant difference in quality of life improvement between the two groups.<sup>248</sup>

Vedantham has emphasized the importance of individualizing treatment to the specific patient, stressing the importance of evaluating bleeding risk in catheter directed thrombolysis.<sup>249</sup> The ATTRACT trial demonstrated that addition of pharmaco-mechanical catheter-directed thrombolysis to anticoagulation does not result in an overall lower risk of any post-thrombotic syndrome (PTS) in patients with proximal deep venous thrombosis (femoro-popliteal and ilio-femoral) and was associated with a modest increase in major bleeding. Nevertheless, the subanalysis of these data shows the benefit in terms of reduced moderate-to-severe PTS and PTS symptomatology severity.<sup>250</sup> Interestingly, no significant changes in the management of acute deep vein thrombosis have been reported following the publication of the ATTRACT trial.<sup>251</sup>

A recently published sub-analysis of the ATTRACT trial looked at the femoro-popliteal cases specifically and demonstrated that, for this subgroup of patients, performing pharmaco-mechanical catheter-directed thrombolysis is of no benefit and is associated with an increased bleeding risk ( $P=0.032$ ).<sup>252</sup> Sub-analysis on the ilio-femoral cases of the ATTRACT trial, showed that pharmaco-mechanical catheter-directed thrombolysis did not influence the overall occurrence of PTS or recurrent venous thromboembolism. However, it significantly reduced early symptoms ( $P<0.01$ ) and, over 24 months, it reduced PTS severity scores ( $P<0.01$ ) and resulted in greater improvement in venous disease-specific quality of life ( $P=0.029$ ).<sup>253</sup>

A review of 6 studies, all comparing experimental groups receiving pharmaco-mechanical thrombectomy and control groups receiving catheter-directed thrombolysis for ilio-femoral deep venous thrombosis, showed that pharmaco-mechanical thrombectomy reduces the severity of post-thrombotic syndrome, thrombus score, duration in hospital, and thrombolysis time compared to catheter-directed thrombolysis.<sup>254</sup> A second systematic review evaluated 15 retrospective investigations and one prospective registry comparing pharmaco-mechanical thrombectomy and catheter-directed



thrombolysis. Of these investigations, seven reported comparative evidence of phamaco-mechanical thrombectomy versus catheter-directed thrombolysis. The review concluded that percutaneous mechanical thrombectomy is a safe and effective in terms of restoration of venous patency, prevention of DVT recurrence, and PTS. Moreover, it found that in comparison to catheter-directed thrombolysis alone, phamaco-mechanical thrombectomy offers a lower risk of post-thrombotic syndrome and bleeding complications. The authors acknowledged the lack of randomized controlled trials on this subject, as previously reported by Cochrane which found no evidence recommending phamaco-mechanical thrombectomy over anticoagulation (alone or with compression stockings), mechanical thrombectomy, thrombolysis, or other endovascular techniques in the management of people with acute deep venous thrombosis of the ilio-femoral vein.<sup>255</sup>

## **2. Chronic deep venous interventional treatment**

Seager identified 14 before-and-after endovenous stenting for iliac vein obstruction studies, 1 controlled before-and-after investigation, and 1 case series. The analysis showed a weak quality of evidence in support of the iliac stenting, but concluded that intervention was safe. A meta-analysis was not feasible because of data heterogeneity.<sup>256</sup>

One small randomized trial has evaluated stenting versus medical treatment for iliac venous obstruction >50% at the intravascular ultrasound (IVUS). Outcome measures were VAS pain score, Venous Clinical Severity Score, and 36-Item Short Form Health Survey quality of life questionnaire. The investigation included also stent integrity, migration, and patency rates at 6 months. The results showed that stenting is safe and provides effective relief of symptoms and improvement in quality of life compared with medical treatment alone in symptomatic patients.<sup>29</sup>

Rizvi et al reported a 98.6% of stent patency at 2 years in non-thrombotic iliac vein lesions.<sup>257</sup>

It should be noticed that in the same year it was confirmed that the loss of stent patency due to stent-related issues like kinking or tapering is hardly ever seen in short-term follow-up. Yet, the same

publication reported complications in the 12 months follow-up in up to 39% of cases, so pointing out the need of further proper investigations on the topic.<sup>258</sup>

## **DISCUSSION**

Finding the proper outcome measure is mandatory in both acute and chronic deep venous disease management. As previously reported for example, CAVENT trial demonstrated an improvement in high stent patency rates and reduced incidence of PTS development, but no difference in quality of life.<sup>248</sup> Before significant evidence-based data on the topic are produced, caution should be paid in not elevating the recommendation grade for early thrombus removal. The same definition of venous obstruction is still in need of international consensus on its definition. In a 2019 editorial, the same supine ultrasound assessment position has been questioned in iliac compression screening, considering the possibility of a stenosis resolution in the semi-seated position.<sup>259</sup> Considering a >50% stenosis at the IVUS investigation as determinant parameter for treatment indication is extremely questionable. As reported by the VIDIO trial, IVUS is more sensitive for assessing treatable ilio-femoral vein stenosis compared with multiplanar venography. Its use leads to possible revised treatment plans with a potential for improved clinical outcome.<sup>260</sup> Indeed, a 2018 publication corroborated the conventional definition of a clinically significant ilio-femoral stenosis as a >50% cross-sectional area threshold by IVUS, specifying that, in non-thrombotic lesions, a threshold of >61% diameter stenosis may better predict clinical improvement. Yet the associated positive predictive value for clinical improvement is not enough high to lead to treatment indication, pointing out the still needed identification of clinical criteria for predicting a reliable post-stenting improvement.<sup>261</sup> On this topic a randomized comparative trial is on-going, including also assessment of changes in short form 36 (SF-36) and the Veines-QoL/Sym questionnaires compared with conventionally treated patients.<sup>262</sup> The importance of proper iliac obstruction definition has been elegantly demonstrated by an investigation on healthy subjects undergoing iliac veins angiography: 80% of the study population had at least two signs of May-Thurner compression and 15% had collaterals activation. In a national survey among specialists, 55% considered

the angiographic sign of >50% compression as indication to treatment.<sup>263</sup> Then, IVUS results to be an excellent tool for guiding the procedure, rather than for leading to the treatment indication. In conclusion, considering the paucity of properly designed investigations on the topic, as pointed out by Seager revision, high recommendations grade should be avoided in the current guidelines.<sup>256</sup>

Looking at the number of patients treated per hospital in the available multi-center analysis, a paucity of cases per recruiting institution is easily noticed, so bringing up the further bias of data collections performed by health professionals with limited experience. Only centers with proper training should be included in future analysis.

An extreme focus on objective measurements such as stenotic pressure values and symptomatology validated assessment is mandatory for proper advancement in chronic deep venous disease understanding and management. In particular a validated outcome measure tool should be created, potentially even before than running other investigations deprived of sound endpoints. Indeed Venous Clinical Severity Score and Villalta score have already been reported as suboptimal in this aspect, particularly considering the lack of venous claudication report, one of the main symptoms in this type of patients. Moreover, a recent publication by Trinh demonstrated that the use of Villalta for defining PTS may lead to false positive diagnosis in 42% of patients with primary chronic venous disease, so significantly limiting its reliability in the assessments dedicated to ilio-femoral obstruction.<sup>264</sup> The present data urge a significant advancement in research and education on this topic, so to offer the best therapeutic choice to the patient, while avoiding overuse of not perfectly designed outcome measures and potentially related overtreatment.

### **KEY MESSAGES**

- In case of acute deep venous obstruction, among the analysed documents, only SVS/AVF<sup>240</sup> and CHEST<sup>122</sup> report a grade of evidence. The AVF/SVS document<sup>239</sup> recommends pharmaco-mechanical thrombectomy over catheter directed pharmacologic thrombolysis alone, while CHEST<sup>10</sup> recommends anticoagulant therapy alone versus catheter directed thrombolysis.

- European, North and South American guidelines are generally agreeing in indicating percutaneous transluminal angioplasty (PTA) and stenting only for severely symptomatic patients.
- Subanalysis on the ilio-femoral cases of the ATTRACT trial, showed that pharmaco-mechanical catheter-directed thrombolysis did not influence the overall occurrence of PTS or recurrent venous thromboembolism. However, it significantly reduced early symptoms ( $P<0.01$ ) and, over 24 months, it reduced PTS severity scores ( $P<0.01$ ) and resulted in greater improvement in venous disease-specific quality of life ( $P=0.029$ ).<sup>253</sup>
- No clear evidence can recommend pharmaco-mechanical thrombectomy over anticoagulation (alone or with compression stockings), mechanical thrombectomy, thrombolysis, or other endovascular techniques in the management of people with acute deep venous thrombosis of the iliofemoral tract.
- A proper score to evaluate post-thrombotic syndrome and ilio-femoral recanalization success is needed.

### **SUGGESTED RESEARCH TOPICS**

- Randomized controlled trials comparing pharmaco-mechanical thrombectomy and catheter-directed thrombolysis.
- A proper score to evaluate post-thrombotic syndrome and ilio-femoral recanalization success is needed.
- International consensus on proper definition of chronic venous obstruction and related assessment protocol.

## **8. VENOUS ACTIVE DRUGS**

### **TOPICS**

- Venous active drugs (VAD) for venous symptoms & signs
- VAD indications for venous ulcer

## **ANALYSED GUIDELINES**

- **AUSTRALIA 2011:** Australian Wound Management Association & New Zealand Wound care society.<sup>265</sup>
- **USA 2011:** American Venous Forum (AVF)/ Society of Vascular Surgery (SVS) guidelines.<sup>2</sup>
- **USA 2014:** SVS/AVF Management of venous leg ulcers: clinical practice guidelines.<sup>32</sup>
- **EUROPE 2015:** European Society of Vascular Surgery (ESVS). Management of Chronic Venous Disease: Clinical Practice Guidelines.<sup>6</sup>
- **UK 2013-2016:** NICE guidelines.<sup>40</sup>
- **LATIN AMERICA 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>
- **EUROPE 2016:** European dermatology forum. Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers.<sup>266</sup>
- **GLOBAL 2018:** International Union of Phlebology (UIP), International Union of Angiology (IUA), Cardiovascular Disease Educational and Research Trust, European Venous Forum (EVF), Management of chronic venous disorders of the lower limbs. Guidelines according to Scientific Evidence. Part I.<sup>11</sup>

## **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

Venous active drugs (VAD) are not globally defined with precision, generally being identified with substances acting on the venous system and particularly addressed to the management of lower limb chronic venous insufficiency and venous thrombosis. No recommendations on VAD were found in the NICE guidelines.<sup>40</sup>

### **1. VAD indications for venous symptoms**

As reported in Tab. 8.1, international guidelines are differing in the VAD method analysis.

AVF/SVS American ones report a list of drugs indicated all with the same recommendation grade (2B),<sup>2</sup> while the European ones indicate them with a 2aA grade without specifying which substances.<sup>6</sup> On the other side, Latin America guidelines are providing a list of drugs with specific grade of evidence per

each substance, but without specifying the dedicated symptom/signs.<sup>8</sup> To the contrary, 2018 global guidelines are providing specific recommendation grades per each drug, together with the related symptom/signs.<sup>11</sup> The above described data heterogeneity makes a comparison among evidence grades impossible. It is noteworthy how the general indication to VAD prescription for venous symptoms varies from 2B to 1A in the different guidelines.<sup>2,6,8,11,32,40,265,</sup>

## 2. VAD indications for ulcer management

Similarly to the indication for venous symptoms, VAD are recommended for ulcer management with different recommendation grades by the international guidelines.

The mainly considered drugs are micronized purified flavonoid fraction (MPFF), sulodexide, rutoside and pentoxifylline. Pentoxifylline is not recommended for routine use by the ESVS guidelines<sup>6</sup> while it is indicated by the global 2018 guidelines<sup>11</sup> with an A level of evidence.

MPFF is indicated with a 1B grade of evidence by both the SVS/AVF 2014<sup>2</sup> and Latin America<sup>8</sup> guidelines, while the ESVS<sup>6</sup> document recommend it with a 2aA grade and the global 2018<sup>11</sup> guidelines with an A level.

These latter two groups<sup>6,11</sup> indicate sulodexide with the same grade of evidence. ESVS<sup>6</sup> document is not recommending ASA use as primary treatment, but it states its possible use in case of resistant ulcers (grade 3C).

	USA SVS/AVF 2011	EUROPE ESVS 2015	LATAM 2016	GLOBAL UIP,EVF,IUA 2018
<b>PAIN</b>	Diosmin, Hesperidine, Horse chestnut,MPFF, Rutosides, Sulodexide (2B)	2aA (no drugs mentioned)	Generally indicated from C2 – C6 Calcium Dobesilate (2B) Diosmin (2C) Ginko Biloba (2C) Oxerutins (not specified) MPFF (1B) Ruscus (2B) Ruthosides (2B) Soludexide (no grading) Vitis vinifera (2B)	Calcium Dobesilate (2B), Horse Chestnut (1A), MPFF (1A), Oxerutins (1A), Ruscus (1A)
<b>HAEVINESS</b>				Calcium Dobesilate (2A), MPFF (1A), Ruscus (1A)
<b>SWELLING</b>	Diosmin, Hesperidine, Horse chestnut,MPFF, Rutosides, Sulodexide (2B)			MPFF (1A), Ruscus (1A)
<b>FUNCTIONAL DISCONFORT</b>				Calcium Dobesilate (2B), MPFF (1A)
<b>LEG FATIGUE</b>				Ruscus (1B)
<b>CRAMPS</b>				MPFF (1B), Oxerutins (1B),

				Ruscus (2B-C)
<b>PARESTHESIA</b>				Calcium Dobesilate (2B), MPFF (2B-C), Ruscus (1A)
<b>BURNING</b>				MPFF (2B-C)
<b>PRURITUS</b>				Horse Chestnut (1A), Ruscus (2B-C)
<b>REDNESS</b>				MPFF (1B)
<b>SKIN CHANGES</b>				MPFF (1A)
<b>EDEMA (ankle region)</b>				Calcium Dobesilate (2A), Horse Chestnut (1A), MPFF (1B), Ruscus (1A)
<b>QUALITY OF LIFE</b>				MPFF (1A)

**Tab. 8.1: Recommendations for venous active drugs for venous symptoms and signs.** International guidelines are differing in the VAD method analysis. AVF/SVS American ones report a list of drugs indicated all with the same recommendation grade (2B),<sup>2</sup> while the European ones indicate them with a 2aA grade without specifying which substances.<sup>6</sup> On the other side, Latin America guidelines are providing a list of drugs with specific grade of evidence per each substance, but without specifying the dedicated symptom/signs.<sup>8</sup> To the contrary, 2018 global guidelines are providing specific recommendation grades per each drug, together with the related symptom/signs.<sup>11</sup>

	USA SVS/AVF 2011	USA SVS/AVF 2014	EUROPE ESVS 2015	LATAM 2016	GLOBAL UIP,EVF,IUA 2018
<b>MPFF</b>	<b>2B</b>	<b>1B</b>	<b>2aA</b>	<b>1B</b>	<b>A</b>
<b>Sulodexide</b>	NOT REPORTED but recommenden in the 2006 American College of Chest Physician guidelines (grade 2B)		<b>2aA</b>	Recommended (no grade)	<b>A</b>
<b>Diosmin</b>				<b>2C</b>	
<b>Rutosides, hesperidine (HMC)</b>				<b>2B</b>	<b>B</b>

Horse chestnut seed extract (Aescin)			Routine use is not recommended <b>3B</b>	<b>2C</b>	
Calcium Dobesilate				<b>2B</b>	
Pentoxifylline	2B	1B	Routine use is not recommended <b>3B</b>	<b>2B</b>	<b>A</b>
Acetyl-salicylic acid			Not recommended but it may be considered for resistant ulcer <b>3C</b>		

**Tab. 8.2: International recommendations on venous active drugs for venous ulcer management.**

The mainly considered drugs are micronized purified flavonoid fraction (MPFF), sulodexide, rutoside and pentoxifylline. Pentoxifylline is not recommended for routine use by the ESVS guidelines<sup>6</sup> while it is indicated by the global 2018 guidelines<sup>11</sup> with an A level of evidence.

MPFF is indicated with a 1B grade of evidence by both the SVS/AVF 2014<sup>2</sup> and Latin America<sup>8</sup> guidelines, while the ESVS<sup>6</sup> document recommend it with a 2aA grade and the global 2018<sup>11</sup> guidelines with an A level. These latter two groups<sup>6,11</sup> indicate sulodexide with the same grade of evidence.

### **SIGNIFICANT RECENT DATA RELATED TO THE MEETING DISCUSSION**

In 2017 an American systematic review on MPFF concluded that the general level of evidence supports its recommendation for the healing of venous ulcers and for the reduction in symptoms of chronic venous disease.<sup>267</sup>

In 2018 a systematic review demonstrated that sulodexide significantly reduces the recurrence of venous-thromboembolism after discontinuation of anticoagulation treatment.<sup>268</sup>

In the same year a Cochrane analysis on Rutosides reported no significant evidence supporting its use in post-thrombotic syndrome symptoms control compared to placebo or graduated compression stockings.<sup>269</sup>



In 2019 a review on sulodexide pointed out its anti-inflammatory and anti-thrombotic actions supporting its clinical benefit throughout the chronic venous disease spectrum.<sup>270</sup>

In 2018 and 2019, two reviews on MPFF supported its use in all the 6 CEAP clinical classes.<sup>271,272</sup>

Because of the significant amount of literature on VAD for venous ulcer treatment has unclear risk of bias for randomization, allocation concealment, and blinding, a 2016 systematic review concluded that pentoxifylline (400 mg, 3 times a day) was the only drug showing promise as an effective adjunct to venous ulcer treatment.<sup>273</sup> Yet, pentoxifylline is currently unlicensed and the ESVS European guidelines recommend against its use.<sup>6</sup>

In the same year, a Cochrane analysis on phlebotonics (rutosides, hidrosmine and diosmine, calcium dobesilate, centella asiatica, aminaftone, french maritime pine bark extract and grape seed extract) for venous insufficiency concluded that VAD may have a beneficial effect on oedema and on some signs and symptoms related to chronic venous insufficiency (trophic disorders, cramps, restless legs, paresthesia) when compared to placebo, but can also produce adverse effects. No difference was found in comparison of phlebotonics with placebo for venous ulcer healing. The same document pointed out the need of more high-quality randomized comparative trials focused on clinically important outcomes in order to improve the evidence.<sup>274</sup>

In 2017 the combination of sulodexide and diosmin-hesperidin micronized purified flavonoids was demonstrated to be effective in accelerating ulcer healing, controlling pain and improving lipodermatosclerosis.<sup>275</sup>

## **DISCUSSION**

A fundamental aspect to be taken into consideration both in the VAD for venous symptoms and venous ulcer management is the current lack of properly validated tools for objective data reporting. This is particularly evident for example in the quality of life and symptoms assessment. For data analysis homogeneity future research should also carefully assess the impact of musculo-skeletal and postural condition potentially confounding the patient reported outcome in terms of symptomatology. Weight

bearing analysis data report should be taken into consideration for example. Of significant importance is the absence of evidence-based data on the timing between the initiating VAD and the minimum period of VAD treatment for guaranteeing its effectiveness. VAD categories represents a major confounding factor in itself, considering that drugs with significantly different pharmacokinetics and pharmacodynamics are included in the same group, making the vast majority of international guidelines currently inaccurate for any meaningful comparisons. Future investigations should also address the potential bias of the patient psychological component together with the wide range in symptoms and quality of life report: the lack of proper description tool in this context has been recently published both related to varicose veins<sup>276</sup> and ulcer conditions.<sup>277</sup> Last but not least, clear correlations among hemodynamics changes and VAD use are missing in the literature, while they should be planned for a better understanding of the venous bio-signaling and the related clinical impact. In conclusion, the use of VAD for venous symptoms and venous ulcer healing enjoy a growing interest in their applications, yet VAD are deprived of a proper research methodology that would otherwise provide strong and globally shared recommendations for many related topics in the treatment of chronic venous disease. Future well-designed investigations involving a multi-specialty approach and using properly validated tools for homogeneous and unbiased assessment are strongly encouraged.

### **KEY MESSAGES**

- Venous active drug specific definition is missing leading to bias in the recommendations dedicated to different substances for venous symptoms and signs.
- Micronized purified flavonoid fraction and sulodexide are the main drugs recommended in ulcer management, yet with different grade of evidence in the different guidelines.

## **SUGGESTED RESEARCH TOPICS**

- Randomized comparative studies assessing the effect of specific venous active drugs in homogeneous populations with the support also of basic-science analysis of the same drug effect on the venous inflammation.

## **9. VENOUS ULCER MANAGEMENT**

### **TOPICS**

- Venous ulcer management: compression, wound dressings, antibiotics, interventional procedures.

### **ANALYSED GUIDELINES**

- **AUSTRALIA 2011:** Australian Wound Management Association & New Zealand Wound care society.<sup>265</sup>
- **USA 2011:** American Venous Forum (AVF)/ Society of Vascular Surgery (SVS) guidelines.<sup>2</sup>
- **USA 2014:** SVS/AVF Management of venous leg ulcers: clinical practice guidelines.<sup>32</sup>
- **EUROPE 2015:** European Society of Vascular Surgery (ESVS). Management of Chronic Venous Disease: Clinical Practice Guidelines.<sup>6</sup>
- **UK 2013-2016:** NICE guidelines.<sup>40</sup>
- **LATIN AMERICA 2016:** Guías latinoamericanas de terapéutica para la patología venosa.<sup>8</sup>
- **EUROPE 2016:** European dermatology forum. Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers.<sup>266</sup>
- **GLOBAL 2018:** International Union of Phlebology (UIP), International Union of Angiology (IUA), Cardiovascular Disease Educational and Research Trust, European Venous Forum (EVF), Management of chronic venous disorders of the lower limbs. Guidelines according to Scientific Evidence. Part I.<sup>11</sup>

## **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

International guidelines recognize the pivotal role of appropriate compression in ulcer healing and recurrence prevention. At the same time no clear recommendations can be found for the most appropriate compression methodology (type, duration, and dose). The role of compression in venous ulcer healing and recurrence prevention has been extensively reported in this document session dedicated to bandaging and graduated elastic stockings. Table 9.1 summarizes the recommendations from the different societies.

## 9. VENOUS ULCER MANAGEMENT

	USA AVF/SVS 2011 (GRADE)	AUSTRALIA 2011 (A-D)	UK NICE 2013-2016	USA AVF/SVS 2014 (GRADE)	EUROPE ESVS 2015 (I-III; A-C)	LATAM 2016 (GRADE)	EUROPEAN DERMATOLOGY FORUM 2016 (I-IV)	EUROPE 2018 (GRADE)	USA AVF/SVS/AVL 2019 (GRADE)
<b>Healing</b>	<b>1B</b>	<b>B</b> Zinc bandage to promote epithelialisation of a healthy granulated superficial ulcer	Compression is recommended  <b>Juxta CURES</b> (2015) and <b>COBAN 2</b> (2018) recommended	<b>1A</b> <b>2B</b> Multicomponent bandage vs single-component  <b>2C</b> IPC when standard compression has failed or is not feasible	<b>IA</b> (specific bandage)  <b>IIaB</b> At least 40 mmHg  <b>IA</b> Compression bandage as initial treatment to promote healing  <b>IIaB</b> <b>IPC after 6 month when the other have failed</b>	<b>1B</b>	<b>I</b> No evidence that a particular type of bandage is the best. High pressure is more effective than low compression  4 layer bandage if inexperienced in high pressure  Short stretch the best to reduce edema  Graduated elastic stockings whenever size and level of exudation allow it	<b>1A</b>	<b>1B</b>
<b>Recurrence Prevention</b>	<b>1A</b>	<b>B</b>		<b>2B</b>	<b>IB</b>	<b>IA</b>	<b>II</b>	<b>1A</b>	<b>1B</b>

**Tab. 9.1: International recommendations for compression for venous ulcer healing and recurrence prevention.** While compression is generally recognized in its main role for venous ulcer healing and recurrence prevention, a significant heterogeneity in the grade of evidence is detected among different guidelines.

	USA AVF/SVS 2011 (GRADE)	AUSTRALIA 2011 (A-D)	UK NICE 2013-2016	USA AVF/SVS 2014 (GRADE)	EUROPE ESVS 2015 (I-III; A-C)	LATAM 2016 (GRADE)	EUROPEAN DERMATOLOGY FORUM 2016 (I-IV)
<b>WOUND DRESSINGS</b>	Not reported	<b>B</b> No specific dressing product is superior for reducing healing time in VLU. Select dressings based on clinical assessment of the ulcer, cost, access and patient/health professional preferences.	Simple non-adherent dressing are recommended in the management of venous leg ulcer.	<b>2C</b> topical dressing that will manage venous leg ulcer exudate and maintain a moist, warm wound bed.  <b>2B</b> primary wound dressing that will absorb wound exudate produced by the ulcer (alginates, foams) and protect the periulcer skin.	<b>IbA</b> Wound dressing may be considered to promote healing of venous ulceration  <b>IbC</b> Zinc dressings and cadexomer iodine may be considered to promote venous ulcer healing as first and second choice, respectively	Not reported	<b>I</b> Hydrocolloids not more effective than gauze  <b>III</b> There are indications that pain in combined ulcers is reduced by either a hydrocolloid or a foam dressing  <b>IV</b> modern wound dressings are better than the traditional gauzes in wound healing

**Tab. 9.2: International recommendations on wound dressings for venous ulcer.** Lack of homogeneity in the grade of evidence and the absence of a sound indication for their prescription is evident. The European Dermatology Forum document is the only one, among the analysed published guidelines, suggesting that modern wound dressings are better than traditional gauzes in wound healing.<sup>266</sup>

International recommendations on topical dressings for venous ulcer are reported in 9.2, highlighting the lack of homogeneity in the grade of evidence and the absence of a sound indication for their prescription. The European Dermatology Forum document is the only one, among the analysed published guidelines, suggesting that modern wound dressings are better than traditional gauzes in wound healing.<sup>266</sup> Yet this indication has the lowest level of evidence, indicating low quality evidence and need for further investigations for proper recommendations.

Indications for antibiotic use in venous ulcer management is quite homogeneous among the analysed international documents, recommending the use of systemic therapy only in cases of clinical signs of infection. A general agreement among the different guidelines is present in not using anti-microbial products routinely or in colonized wounds. On the contrary, lack of homogeneity in the grade of

evidence for non-systemic infections in venous ulcer bed can be noticed in the different guidelines recommendation (Table 9.3).

	USA AVF/SVS 2011 (GRADE)	AUSTRALIA 2011 (A-D)	UK NICE 2013-2016	USA AVF/SVS 2014 (GRADE)	EUROPE ESVS 2015 (I-III; A-C)	LATAM 2016 (GRADE)	EUROPEAN DERMATOLOGY FORUM 2016 (I-IV)
<b>ANTIBIOTICS</b>	Not reported	<b>B</b> Systemic should not be used in standard care in absence of clinical infection	<b>C</b> Systemic not be used unless there is evidence of clinical infection. Insufficient evidence to recommend the use of silver dressings in infected or contaminated wounds	<b>2A</b> Against topical antimicrobial in non infected (2A) and colonized (2C) venous ulcers. <b>1B</b> Systemic for cellulitis <b>1C</b> Systemic (first 2 weeks orally) in case of clinical infection <b>2C</b> Against topical antimicrobial for infected wounds	<b>IIIb</b> Zinc, oral antibiotics, horse chestnut seed extract and pentoxifilline is not recommended. Antibiotics only in case of clinical infection, not for colonization.	Oral or systemic in signs of erysipelas and cellulitis.	<b>III</b> Systemic appeared to be meaningless without sign of active infection Topical antibiotics have no place in the treatment <b>IV</b> Topical 0.5–1% acetic acid solution may be used to treat wounds contaminated with pseudomonas. However, a scientific basis is lacking for this.

**Tab. 9.3: International recommendations on antibiotic use for venous ulcer management.**

Indications for antibiotic use in venous ulcer management is quite homogeneous among the analysed international documents, recommending the use of systemic therapy only in cases of clinical signs of infection. A general agreement among the different guidelines is present in not using anti-microbial products routinely or in colonized wounds.

	USA AVF/SVS 2011 (GRADE)	AUSTRALIA 2011 (A-D)	UK NICE 2013-2016	USA AVF/SVS 2014 (GRADE)	EUROPE ESVS 2015 (I-III; A-C)	LATAM 2016 (GRADE)	EUROPEAN DERMATOLOGY FORUM 2016 (I-IV)
<b>VENOUS PROCEDURE</b>	<b>1A</b> ablation of the incompetent vein	Possible beneficial effect, but not enough evidence to overcome standard care.	Patients with chronic venous leg ulcer and superficial venous reflux should be considered for superficial venous surgery for recurrence.	<b>1B</b> For healing <b>1C</b> For recurrence risk reduction	<b>IB</b> The possibility of active venous intervention should be explored for venous ulcer healing  <b>IIaB</b> Foam sclerotherapy as primary treatment in elderly and frail patients with venous Ulcers.	<b>1 A</b> ablation of the insufficient superficial venous system plus compression to reduce recurrence  <b>2B</b> Treatment of the incompetent perforating vein located around an open or close ulcers  <b>2C</b> SEPS, ultrasound – guided sclerotherapy or thermoablation for the incompetent perforating vein treatment.	<b>I</b> Short Stripping + SEPS for combined superficial and perforator insufficiency  <b>III</b> Sclero-compression therapy to improve healing

**Tab. 9.4: Indications to interventional procedures for venous ulcer management.** While a general agreement toward the application of procedures in venous ulcer management exists in all the guidelines evaluated, a significant heterogeneity in the reported grade of evidence is detected.

Table 9.4 includes the different indications to venous interventional treatment for venous ulcer healing and venous ulcer recurrence reduction. While a general agreement toward the application of procedures in venous ulcer management exists in all the guidelines evaluated, a significant heterogeneity in the reported grade of evidence is detected.



	USA AVF/SVS 2011 (GRADE)	AUSTRALIA 2011 (A-D)	UK NICE 2013-2016	USA AVF/SVS 2014 (GRADE)	EUROPE ESVS 2015 (I-III; A-C)	LATAM 2016 (GRADE)	EUROPEAN DERMATOLOGY FORUM 2016 (I-IV)
<b>NEGATIVE PRESSURE THERAPY</b>	Not reported	Not enough evidence	Not enough evidence	<b>2C</b> Against primary use	Not reported	Not reported	<b>III</b> in some trials, in which negative pressure treatment led to faster wound healing were of low power
<b>SKIN GRAFTING</b>		<b>B</b> Consider bi-layered, bioengineered skin grafts to promote healing in persistent VLU		<b>2B</b> against split-thickness skin grafting as primary therapy  <b>2B</b> recommended for selected large venous leg ulcers that have failed to show signs of healing with standard care for 4 to 6 weeks	Not reported	Not reported	<b>I</b> the additional value of (various sorts) 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

**Tab. 9.5: International recommendations for negative pressure therapy and skin grafting in wound management.** International guidelines are in agreement with not recommending negative pressure therapy and skin grafting for venous ulcer as primary treatment, considering the paucity of evidence-based data for these modalities.

As reported in table 9.5, international guidelines are in agreement with not recommending negative pressure therapy and skin grafting for venous ulcer as primary treatment, considering the paucity of evidence-based data for these modalities.

### SIGNIFICANT RECENT DATA RELATED TO THE MEETING DISCUSSION

In a 2018 Cochrane analysis pointed out the need of more research to determine whether particular dressings or topical agents improve the probability of healing venous ulcers.<sup>278</sup>

In the same year, in United Kingdom, the EVRA trial demonstrated a faster venous ulcer healing and a longer median ulcer-free time following endovenous ablation and compression versus compression alone, so that currently NICE recommends early endovenous treatment in patients with venous ulcers.<sup>279</sup>

Interestingly, no significant changes in the practice patterns of British physicians tendency to recommend interventional treatment has been reported. The possible explanation of this finding has been linked with the heterogeneity with other guidelines recommendation and with the possible knowledge gap of the new indication.<sup>280</sup>

Negative pressure therapy and skin grafting remain deprived of significant evidence leading to strong recommendation for venous ulcer treatment. In particular, Cochrane Reviews have stated the absolute need of future investigation assessing the effectiveness of negative pressure therapy.<sup>281</sup>

In 2016 a study evaluating the combination of vacuum-assisted closure and skin grafting resulted in not superior results compared to conventional dressing, and associated with more complications.<sup>282</sup>

On the contrary, in 2017 a published systematic review on skin grafting reported promising outcome in venous ulcer healing by autologous split-thickness skin grafting.<sup>283</sup>

In addition, in 2017, the future potentials of autologous-derived stem-cells in venous ulcer treatment was described.<sup>284</sup> Future work and trials are needed before recommendations for autologous stem cells can be recommended for venous ulcer treatment.

## **DISCUSSION**

International guidelines on venous ulcer management have significant variability in the published literature, exemplifying the difficulties with the creation of homogeneous global recommendations.<sup>285</sup>

Both for VAD and venous ulcer care, future international recommendations should focus on a standardized assessment of the same available evidence. A dedicated approach for standardization is represented by the Appraisal of Guidelines for Research and Evaluation (AGREE) tool: an analysis instrument for developmental process and reporting quality of guidelines to address the issue of variability in the quality of practice guidelines. Such analysis deals with the methodological rigor of recommendations formulation and clarity of presentation, without assessing the accuracy of the same indications. A recent publication applied AGREE on the currently available international guidelines for venous ulcer management, pointing out the lack of elements in the methodology.<sup>286</sup>

Another major bias easily recognized in the analysed literature on this topic is the inclusion of usually uncomplicated and/or small size ulcers, so creating the confounding factor of an easier benefit from VAD and a more difficult advantage of dedicated dressings. Scores related to wound care in venous ulcers, such as the one introduced by Falanga,<sup>287</sup> are available and their use should be included in future investigations to enhance the homogeneity among the different study populations when evaluating treatment related outcomes.

### **KEY MESSAGES**

- Graduated compression is recognized as pivotal in ulcer treatment by all the analysed guidelines. Yet, no clear indications are found regarding the best type, duration and dose of compression.
- A general agreement among the different guidelines is present in not using anti-microbial products routinely or in colonized wounds.
- The European Dermatology Forum document is the only one, among the analysed published guidelines, suggesting that modern wound dressings are better than traditional gauzes in wound healing.<sup>243</sup>
- Different grade of evidence are reported in indications to treatment for venous ulcer management.

### **SUGGESTED RESEARCH TOPICS**

- Randomized comparative trial focused on the real need of advanced dressings in venous ulcer management.
- Investigations assessing the real advantage of negative pressure therapy and regenerative cellular therapy.
- Cost-effectiveness analysis in proper compression for ulcer management, randomizing bandaging, adjustable compressions wraps and graduated compression stockings.

## **10. LOWER LIMB LYMPHEDEMA**

### **TOPICS**

- Conservative management of lymphoedema
  - a. Complex decongestive physiotherapy
  - b. Graduated compression
  - c. Intermittent pneumatic compression
  - d. Mesotherapy in lymphedema
- Surgical management of lymphoedema

### **ANALYSED GUIDELINES**

- **GLOBAL 2006:** International Lymphoedema Framework. International consensus: best practice for the management of lymphoedema.<sup>288</sup>
- **ITALY 2007:** Lymphedema Italian guidelines<sup>289</sup>
- **GLOBAL 2013:** International Union of Phlebology (UIP) Diagnosis and treatment of primary lymphedema. Consensus document<sup>290</sup>
- **ITALY 2015:** Italian Society for the study of Vascular Anomalies (SISAV). Vascular Anomalies Guidelines<sup>291</sup>
- **GLOBAL 2015:** International Union of Angiology (IUA) - International Society for Vascular Investigation (ISVI) Consensus for diagnosis guideline of chronic lymphedema of the limbs.<sup>292</sup>
- **GLOBAL 2016:** International Society of Lymphology (ISL)<sup>293</sup>
- **ITALY 2016:** Italian society of phlebology- Italian society of vascular and endovascular surgery (SIF-SICVE)<sup>78</sup>
- **LATIN AMERICA 2017:** Latin American consensus for the treatment of lymphedema.<sup>294</sup>
- **NETHERLANDS 2017:** Dutch lymphedema guidelines.<sup>295</sup>
- **UK 2018:** Lymphoedema BMJ Best Practice 2018.<sup>296</sup>

## **ANALYSIS OF CURRENT INTERNATIONAL RECOMMENDATIONS**

Despite growing awareness of the burden of lymphedema, with up to 250 million people affected worldwide,<sup>297</sup> clear evidence based investigations and related recommendations are lacking in the literature.

Moreover, the analysis of international guidelines reveals marked heterogeneity in recommendations related to the same indications, with only a limited number of documents reporting grades of evidence and levels of recommendation (e.g. UIP 2013,<sup>290</sup> IUA-ISVI 2015,<sup>292</sup> SIF – SICVE 2016<sup>78</sup>).

As reported by the UIP 2013 consensus document,<sup>290</sup> numerous staging systems have been proposed, though none of these comprehensively characterizes lymphedema presentations.

The ISL<sup>293</sup> and LATAM<sup>294</sup> consensus documents, despite being published in the same year, present two different staging systems. ISL,<sup>293</sup> in accordance with BMJ 2018,<sup>296</sup> reports 4 stages (subclinical, early fluid accumulation, oedema independent of leg elevation, elephantiasis), while LATAM<sup>294</sup> identifies 5 stages (edema, fibrotic edema, fibrosclerosis, sclerosis, elephantiasis).

Complex Decongestive Physiotherapy (CDP) is universally recognized as pivotal in lymphedema management by all guidelines, with the UIP<sup>290</sup> and LATAM<sup>8,294</sup> documents agreeing on 1B level of evidence. The BMJ 2018<sup>296</sup> document is an exception, highlighting the unclear benefit of CDP compared to compression and self-massage due to the amount of time, effort and resources required to deliver it. At the same time, CDP in itself presents a definition that varies among the different international documents, with just the Dutch guidelines<sup>295</sup> and the Lymphedema Association of North America Position Statement<sup>298</sup> specifying the requirements for being considered a specialized treatment center and a specialist, respectively. CDP nomenclature is variable despite reference to the same subject. For example, CDP, despite officially referred to as “Complex Decongestive Therapy” by ISL 2016,<sup>293</sup> was also defined as ‘*intensive therapy*’, ‘*combined physiotherapy*’, ‘*Decongestive Lymphatic Therapy*’ and ‘*Combined Physical Lymphoedema treatment*’ in the different society documents. The importance of a graduated compression is recognized by all guidelines, with the most recent 2018 European

consensus statement upgrading the recommendation to level 1A<sup>80</sup>, which is in contrast with the 1B recommendation reported by the 2016 SIF- SICVE<sup>78</sup> and UIP 2013<sup>290</sup> guidelines. Regarding the level of compression, ISL 2016<sup>293</sup> recommends the highest tolerated compression between 20 to 60 mmHg, while BMJ 2018<sup>296</sup> recommends at least 30 mmHg.

Among guidelines there is agreement in supporting intermittent pneumatic compression (IPC) as part of the therapeutic protocol, though never as a “stand-alone” treatment. IPC has been shown to reduce lower limb volume by up to 69%,<sup>102</sup> yet the evidence is limited by studies reporting the use of different devices and protocols, resulting in a 2C recommendation according to UIP 2013<sup>293</sup> and 1B according to the Italian 2016 SICVE-SIF guidelines.<sup>78</sup> Little detail regarding timing and pressure levels are reported in the different guidelines, with the exception of the Latin American ones<sup>294</sup> suggesting 1-2 cycles per minute, with pressures between 20 and 40 mmHg. The BMJ guidelines<sup>296</sup> recognize the effectiveness of IPC in reducing limb volumes, but highlight the heterogeneity of the literature in terms of device use and the lack of long-term follow up studies. Injection of substances like hyaluronidase or similar in the subcutaneous tissue by mesotherapy for lymphedema has only been quoted by the ISL 2016<sup>293</sup> and Latin American guidelines,<sup>294</sup> highlighting the unclear benefit of this practice and the potential for harm, for example by representing a possible source for infection in a limb with an altered immunological system. No levels of evidence have been reported regarding pharmacotherapy for lymphedema, with BMJ 2018 concluding it would be best to avoid their use until more evidence is produced.<sup>296</sup> General agreement is reported regarding the use of lymphatic surgery only when conservative management has not been satisfactory. The UIP 2013<sup>290</sup> guidelines are the only ones to specify a timeline of at least 6 months of conservative treatment attempted prior to considering surgical intervention (grade 1C recommendation). The importance of surgery not being a stand-alone treatment modality, and of a multidisciplinary approach, is highlighted in all the guidelines.

## **SIGNIFICANT RECENT DATA RELATED TO THE MEETING DISCUSSION**

According to BMJ 2018,<sup>296</sup> there are two main surgical options for leg lymphedema: excisional and anastomotic procedures. The review by Cormier et al<sup>299</sup> highlights that a number of surgical approaches have demonstrated to be beneficial in selected patients. Nevertheless, these data are based on studies with small patient numbers, non-standardized measurement techniques and lacking long-term follow up. In 2014, Hadamitzky et al's review also highlighted the difficulty in comparing data from diverse studies due to the different lymphoedema definitions and classifications employed. Nonetheless, the review highlighted both the lack of clear evidence supporting lympho-venous anastomosis, and of strong evidence against it; thus, the therapeutic strategy in these patients should not exclude surgery.<sup>300</sup>

A 2017 systematic review by Carl et al reported that the analysis of a total of 12 high quality studies, including 3.074 patients, indicated that lympho-venous anastomosis is the most appropriate technical choice for early to mid-stages of lymphedema, considering the low complication profile and validated success. On the contrary, considerable risks are associated with vascularized lymphnode transfer and this procedure should be reserved only for severe lymphedema (ISL IIB to III). Also, in this revision, the heterogeneity of the included studies is reported, highlighting the lack of head to head comparisons of microsurgical techniques.<sup>301</sup> A recently published study highlighted the importance of appropriate 2-compartment lymphoscintigraphy in order to accurately detect lymphatic flow abnormalities and to plan adequate treatment and eventual surgical repair.<sup>302</sup> With regards to conservative management, adjustable compression wraps are producing preliminary evidence of benefit, providing appropriate pressure with significant lymphedema patient compliance, and evidence that this is suitable for self-management.<sup>303,304</sup>

## **DISCUSSION**

Lack of homogeneity is the current Achilles' heel of modern lymphology. Indeed CDP, graduated and intermittent compression and lymphatic surgery have all demonstrated clear potential for benefit in the treatment of lymphoedema; yet heterogeneity in study population, study methodology (both in CDP delivery and in compression devices) and outcome measurement introduces bias that limits the evidence

base. In 2017<sup>295</sup> the Dutch guidelines highlighted the importance of organizing “chronic care models” able to manage appropriately chronic lymphedema. The same document highlights three phases in the optimal conservative treatment: decongestion, stabilization and maintenance. It is fundamental that these phases are developed and delivered by appropriately trained centers. Another fundamental step forward will be represented by the creation of globally accepted lymphoedema staging systems, and by the establishment of clear therapeutic protocols that can be delivered by appropriately trained healthcare professionals. This has the potential to greatly improve the delivery and care of these patients. For example, in advanced fibrotic stages, compression therapy will not be as satisfactory as in early lymphoedema, while CDP performed by healthcare workers with different training will lead to different outcomes. Whenever managing lymphedema, it is mandatory to make a distinction between primary and secondary cases, which are to be approached differently.<sup>305,306</sup> It should also be considered that secondary cases can actually be manifestations of “latent primary” conditions that become clinically apparent following an acute event. Early diagnosis and characterization of the type of lymphedema are fundamental, and innovative diagnostic tools, such as bioimpedance, can be of assistance in this. It must be highlighted that diuretics, often over-prescribed, are contraindicated in pure obstructive lymphedema. Empirically, it appears there is a future for the role of pharmacotherapy in this field, particularly as increasing knowledge of lymphoedema pathophysiology is gathered; nonetheless, at this stage, clear evidence in this field is lacking. CDP and surgery are not alternatives, rather synergistic approaches in the management of the lymphoedema patient, and appropriate phrasing should be encouraged in the future on this topic: indeed, surgery should complement CDP when the decongestion phase has not been able to reach the best possible outcome, which is different from the usually defined CDP failure. Lymphedema is a chronic condition, often compared to diabetes in terms of mandatory adaptation of patient life-style once appropriate therapy has led to an optimal decongestion. Only following these principles and obtaining optimal patient compliance, it will be possible to guarantee a stable long-lasting therapeutic result.



## **KEY MESSAGES**

- Homogeneous data collection is generally lacking in lymphedema assessment.
- Complex Decongestive Physiotherapy (CDP) definition. GCS is recommended globally, but with different pressure levels.
- Intermittent pneumatic compression (IPC) is generally recognized as part of the therapeutic protocol, though never as a “stand-alone” treatment.
- Mesotherapy for lymphedema has only been quoted by ISL and Latin American guidelines, highlighting the unclear benefit and the potential for harm.
- General agreement is reported regarding the use of lymphatic surgery only when conservative management has not been satisfactory.
- Adjustable compression wraps demonstrated preliminary evidence of benefit.

## **SUGGESTED RESEARCH TOPICS**

- Globally recognized objective staging system and nomenclature for lymphedema.
- Identification of a uniform and internationally recognized training requirement for health professionals involved with lymphedema management.
- CDP cost-effectiveness analysis.
- Intermittent pneumatic compression standardization protocols and investigations using homogeneous devices so to avoid the bias of the different instrumentation.
- Comparative, multicenter, long terms studies of different surgical techniques.
- International consensus on mesotherapy and on pharmacotherapy.

## **11. VENOUS THROMBOSIS MANAGEMENT**

### **TOPICS:**

1. Superficial Venous Thrombosis (SVT)
2. Calf Vein Deep Venous Thrombosis (DVT)
3. Cancer associated DVT
4. Extended low dose anticoagulation treatment to reduce the risk of recurrent DVT

### **ANALYSED GUIDELINES**

- **UK 2012-2015:** National Institute for Health and Care Excellence (NICE).<sup>123</sup>
- **GLOBAL 2013:** International Consensus Statement from combined Cardiovascular Disease Educational and Research Trust, European Venous Forum, North American Thrombosis Forum, International Union of Angiology and International Union of Phlebology (ICS).<sup>241</sup>
- **USA 2016:** American College of Chest Physicians (ACCP).<sup>122</sup>
- **ASIA 2017:** Malaysian VTE prevention and treatment guideline (MOHM).<sup>121</sup>
- **EUR 2018:** European Society of Cardiology guidelines (ESC).<sup>246</sup>

## **CURRENT INTERNATIONAL RECOMMENDATIONS ANALYSIS**

### **1. Superficial Venous Thrombosis**

SVT most commonly occurs in the great saphenous vein (GSV) and its tributaries, and proximity to the sapheno-femoral junction (SFJ) is associated with likelihood of progression to DVT.<sup>307</sup> Few English-speaking guidelines address SVT. Only the International Consensus Statement (ICS) from combined Cardiovascular Disease Educational and Research Trust, European Venous Forum, North American Thrombosis Forum, International Union of Angiology and Union Internationale du Phlebologie and the

American College of Chest Physician's (ACCP) 2012 VTE guidelines offer recommendations on optimal treatment. Both guidelines recommend treatment of SVT  $\leq 3$  cm from the SFJ be treated with systemic anticoagulation (as for a lower extremity DVT) and those  $>3$ cm from the SFJ and  $>3$  cm length with prophylactic dose fondaparinux over low molecular weight heparin (LMWH).<sup>241,308</sup> Treatment duration was recommended to be 45 days (ACCP)<sup>308</sup> or 4 weeks (ISC).<sup>241</sup> The data underlying these recommendations largely arises from the CALISTO trial. This trial, the largest randomized double-blind trial to date, compared outcomes following 45 days of prophylactic fondaparinux versus placebo for SVT treatment. Fondaparinux significantly reduced the rate of DVT/PE by 85% and was associated with lower rates of extension and recurrence without an increased incidence of major bleeding.<sup>309</sup>

## **2. Calf Vein DVT**

Isolated calf vein DVT is a common clinical entity, comprising 30-50% of DVT diagnosed by ultrasound.<sup>310,311</sup> Unlike the treatment of proximal (ilio-femoral and femoral-popliteal) DVT, which has been studied rigorously via multiple randomized control trials over several decades, there is a paucity of trial data to guide therapy for calf vein DVT. Approximately 6% of patients with calf vein DVT not treated with anticoagulation suffered thromboembolic complication in the contemporary CALTHRO trial. In contrast, this has been reported to be as high as 29% in historical series.<sup>312,313</sup> Risk factors associated with thromboembolic complications include positive D-dimer, extensive thrombosis ( $>7$ mm in maximum diameter,  $>5$  cm in length, multiple vessels), proximity to proximal popliteal vein, no identifiable reversible risk factors, active cancer, personal VTE history and inpatient status.

The uncertain natural history and lack of trial data for this common condition are reflected in the heterogeneity of published treatment recommendations. In total, one VTE guideline (ACCP) and two consensus statements (ISC and European Society of Cardiology, [ESC]) address calf vein DVT and range from favouring serial imaging to favouring anticoagulation.<sup>122,241,246</sup> The ACCP guidelines recommend serial imaging unless the patient has severe symptoms or risk factors (as previously listed).<sup>122</sup> The ICS consensus document recommends 3 months of anticoagulation unless a

contraindication is present, under which condition serial ultrasounds are recommended.<sup>241</sup> The ESC recommends a graduated approach: that high risk patients undergo anticoagulation for 3 months, whereas low risk patients be treated with shorter duration (4-6 weeks), prophylactic dose, or followed with serial ultrasound.<sup>246</sup>

### **3. Cancer associated DVT**

Active malignancy represents the strongest VTE risk factors, accounting for significant morbidity and mortality in this vulnerable patient population.<sup>314</sup> Multiple open-labelled trials in the 2000s demonstrated improved efficacy of LMWH over VKAs for prevention of VTE in this patient population. In a recent Cochrane meta-analysis, pooled results of 7 trials confirmed this finding, albeit with no difference in overall survival, bleeding or thrombocytopenia.<sup>315</sup> The robustness and consistency in this data is reflected in 5 VTE guidelines and consensus statements. All five (ISC, ESC, ACCP, NICE, and MOHM) recommend LMWH for initial and long term (3-6 months) therapy of VTE in cancer patients.<sup>121,122,123,241,246</sup> Practical concerns over LMWH in this patient population include the feasibility and quality of life with long-term parenteral therapy and lack of safety and efficacy outcomes with indefinite therapy.

### **4. Extended low dose anticoagulation treatment to reduce the risk of recurrent DVT**

The use of extended low dose anticoagulation therapy for VTE has not been addressed fully in guidelines, as there is insufficient data to make firm recommendations at this time.

Extended anticoagulant therapy is traditionally considered under the following circumstances: previous VTE, thrombophilias associated with a high risk of recurrence and unprovoked (idiopathic) VTE. Unprovoked first-time VTE remains amongst the most difficult clinical scenarios to manage, as one must balance the competing risks and implications of recurrent VTE and major bleeding. D-dimer and repeat duplex testing have both been advocated as useful tests to determine risk of recurrence with cessation of anticoagulation amongst these patients.<sup>122,316</sup> The use of repeat serial lower extremity

ultrasound to determine the state of the thrombosed veins has been studied, with the assumption that if the veins are occluded with fibrotic scar tissue, flow will be sluggish and the risk of recurrent VTE elevated. The data to support these strategies is modest at best, with ISC, ACCP and ESC documents all acknowledging that there may be a role for such investigations, but recognizing that data is insufficient to make a recommendation.<sup>122,241,246</sup> In contrast, the MOHM guidelines recommend against D-dimer or repeat duplex after completion of anticoagulant therapy.<sup>121</sup>

## **SIGNIFICANT NEW DATA RELATED TO THE MEETING DISCUSSION**

### **1. Superficial Venous Thrombosis**

Both fondaparinux and LMWHs are administered subcutaneously, which can be inconvenient, painful and lead to decreased compliance.<sup>317</sup> In recent years, the rapid adoption of direct oral anticoagulants (DOACs) for a variety of indications have naturally lead to the question as to whether DOACs may offer comparable results. This hypothesis was tested recently in the SURPRISE trial, a randomized, open-label trial enrolling 472 patients. A departure from the CALISTO trial, which had excluded patients with history of malignancy treated within the last 6 months, the SURPRISE trial was designed to include patients at highest risk for VTE, including patients with cancer. The rationale for this approach were findings from cost-effectiveness analysis of the CALISTO trial which found that the overall low rate of thromboembolic events translated to high cost with modest benefit (one life saved for 5,000 treated).<sup>318</sup> In SURPRISE, patients were included only if they had a supragenual location and one of the following risk factors associated with a higher rate of thromboembolic complications: age >65 years, male sex, history of venous thromboembolism (VTE), previous cancer and absence of varicose veins.<sup>319</sup> When comparing 6-weeks of prophylactic fondaparinux to daily rivaroxaban (10mg qday), rivaroxaban was non-inferior to fondaparinux in the prevention of DVT, PE, and progression or recurrence of SVT.<sup>243</sup> Rivaroxaban therapy was postulated to be a less expensive and a more patient-friendly treatment for SVT. In the "high risk" SVT patients in this study thromboembolic events

increased after the end of the active treatment in both treatment groups. This was different from Calisto trial with a lower risk profile in the participants. In further studies the question, if "high risk" SVT patients need a prolonged treatment or if higher anticoagulation doses should be investigated.

Certainly, the rising cost of healthcare and the release of the SURPRISE trial have raised several important considerations about the treatment for SVT. Namely, should a SVT prognostic scoring system be adopted, to better select therapy for patients? A prognostic scoring system would take into account characteristics of the SVT (extent of superficial thrombosis, patient related risk factors, risk for progression to VTE), severity of the SVT and potential for VTE, duration of therapy, and socioeconomic considerations. Days of treatment adds to cost, and it would be worthwhile considering a shorter duration of therapy in the next major SVT treatment trial. Finally, patient reported outcomes are notably absent in SVT treatment trials, and in pursuing the most cost-effective therapy, the end consumer (the patient) should not be ignored.<sup>320</sup>

## **2. Calf Vein DVT**

Withholding anticoagulation in outpatients with suspected calf vein DVT if serial compression ultrasound is negative for proximal DVT at baseline and then again at 1 week results in 3 months pooled estimate thromboembolic risk of 0.6%.<sup>321</sup> Given these findings, the recently completed Compression Alone Versus Anticoagulation for Symptomatic Calf Vein Thrombosis Diagnosed by Ultrasonography (CACTUS) trial was performed with the goal of assessing the safety of withholding anticoagulant treatment in patients with isolated symptomatic calf vein DVT at low risk for proximal extension/VTE (no personal VTE history or active malignancy).<sup>322</sup> To date, the CACTUS trial is the only randomized, placebo-controlled study examining calf vein DVT. LMWH did not reduce proximal extension or VTE and resulted in increased bleeding complications. A limitation of this study is that it was underpowered for its endpoints, as only 259 patients enrolled and the calculated power required was 572 patients.

Despite poor enrolment, the CACTUS trial signifies major progress in one of VTE's most debated topics: it represents the first effort to rigorously study treatment algorithms for this common

condition and adds to accumulating data to suggest that avoiding anticoagulation may be a safer and more cost effective option for low risk patients. Data from smaller studies evaluating low risk patients with calf vein DVT suggests that shorter duration (1 month) and intensity (full dose LMWH x1 week and ½ dose for 3 weeks) had a low recurrence and VTE complication rate, raising the provocative question as to whether patients at high risk need to be treated with the same paradigm as proximal DVT.<sup>320</sup> A well-designed clinical trial enrolling high risk patients with differing treatment regimens for calf vein DVT would represent a logical next step. The frustrating question of how to treat the incidental diagnosis of calf vein DVT in an asymptomatic patient with risk factors remains yet to be answered.

### **3. Cancer associated DVT**

Meta-analysis of cancer patients enrolled in phase 3 DOAC trials demonstrated the feasibility and safety of oral therapy in cancer patients, although this analysis was hampered by lack of comparison to LMWHs as the standard of care.<sup>324</sup> Recently, rivaroxaban and edoxaban have been studied in patients with active malignancy. The Hokusai-VTE cancer trial enrolled 1050 patients with cancer associated VTE who were then randomized to the DOAC edoxaban compared to LMWH. Results from this trial demonstrated that the primary event (recurrent DVT or major bleeding) occurred in 12.8% in the edoxaban group and 13.5% in the LMWH group, meeting the endpoint of non-inferiority for DOAC compared to LMWH.<sup>325</sup> Overall, a reduction in recurrent VTE events in the edoxaban group was offset by an increase in bleeding complications. In subgroup analysis, bleeding risk associated with DOAC therapy was higher in patients with primary GI malignancy.<sup>325</sup> A smaller RCT, SELECT-D, evaluated rivaroxaban compared to LMWH in patients with cancer associated VTE with similar findings: recurrent VTE was 4% in the rivaroxaban group versus 11% in the dalteparin group. This was accompanied by an increased rate of major bleeding in patients treated with rivaroxaban.<sup>326</sup> As a result of this new information, the International Society of Thrombosis and Haemostasis, through its subcommittee, has recommended the use of DOACs in patients with cancer associated VTE but without GI cancer and in those with low bleeding risk.<sup>327</sup> What remains unclear is where patient preferences will

align with regards to tolerance for risk, (bleeding versus thrombosis), and whether there is a way to best select patients for a particular treatment regimen. A more nuanced understanding of patient and disease specific risk factors for bleeding may improve therapy selection.

#### **4. Extended low dose anticoagulation treatment**

The advent of the DOACs has reinvigorated the paradigm of low dose anticoagulation to improve the risk-benefit profile of extended therapy via decreased bleeding risk. Historically, treatment with low-dose VKAs resulted in similar bleeding profile to standard therapy.<sup>328</sup> More recently, both treatment and thromboprophylaxis doses of rivaroxaban and apixaban have been shown to be more effective in prevention of VTE recurrence with no increased risk of bleeding compared to placebo or ASA.<sup>329,330</sup> Interestingly, the WARFASA and ASPIRE trials have also demonstrated a reduced risk of VTE recurrence in patients treated with aspirin compared to placebo.<sup>331,332</sup> However, this decrease in the risk of VTE recurrence with ASA was much less than with low-dose DOACs.<sup>330,331</sup> Indeed, network meta-analysis have shown that some DOACs have the most favourable profiles compared to warfarin, and aspirin.<sup>333,334</sup> While evidence exists that lower dose anticoagulants may effectively reduce VTE recurrence, the most effective therapy with the safest treatment profile and lowest cost is still being debated.

## **DISCUSSION**

Following a half century of sluggish progress, anticoagulant treatment for the DVT patient has abruptly become a rapidly evolving, expansive and progressive field. The diverging recommendations by the guidelines and consensus statements reviewed in this conference reflect a rapidly advancing standard of care that can be difficult for even the seasoned clinician to interpret and implement into day to day practice. We have identified the most impactful studies as they relate to SVT, calf vein DVT, cancer associated DVT and extended thromboprophylaxis and identified recent trends in anticoagulation in the context of current standard of care (Table 11.1.). It is our hope that this may serve as a pragmatic guide.



	Current (or Historical) Standard of Care	New Trend
<b>Superficial venous thrombosis</b>	Fondaparinux (1 <sup>st</sup> line) or LMWH (2 <sup>nd</sup> line) for 4-6 weeks	Oral therapy (rivaroxaban) as 1 <sup>st</sup> line Risk stratification for better cost-benefit ratio
<b>Calf vein DVT</b>	Anticoagulation or serial duplex imaging for symptomatic low-risk patients	Serial imaging for symptomatic low risk patients
<b>Cancer associated DVT</b>	LMWH for initial and long term therapy	DOACs for initial and long term therapy in select patients with low bleeding risk
<b>Extended duration therapy for unprovoked VTE</b>	Long term full dose anticoagulation with VKAs	Long term prophylactic dosing with rivaroxaban or apixaban or ASA.

**Tab.11.1: New trends in anticoagulation in venous patients.**

Despite incredible advancements in terms of large scale clinical trials and drug development over the last decade, a multitude of unanswered questions in anticoagulation pharmacy still remain. As oncologic care has progressed towards more targeted therapies, a natural question arises as to whether personalized treatment for DVT should exist? To date, all agents effective against VTE carry significant bleeding risk, but promising data from first in man human selectin inhibition trials suggest that a safer alternative might be possible. Finally, the role of inflammation and innate immunity in the pathogenesis of VTE and its role in therapy remains undefined: what is the mechanism by which statins decrease thrombotic risk? Do the DOACs have the same anti-inflammatory effect as heparins? Has the skin become a forgotten mediator of post thrombotic inflammation? Are glycosaminoglycans an unexplored target in the vein wall and their potential benefits in reducing recurrent VTE and inflammation? These questions highlight important, evolving concepts in the next chapter of venous thrombosis research, and the opportunity for future research to find answers to these important and intriguing questions in the hope to reduce VTE potential and recurrence, while lowering bleeding risk, and always ascertaining the value and benefit to our patients.

## **KEY MESSAGES**

- International guidelines recommendations for superficial venous thrombosis management are limited and heterogeneous.
- Recommendations for distal DVT anticoagulation are extremely heterogeneous in the different guidelines.
- All analysed guidelines recommend LMWH for initial and long term (3-6 months) therapy of VTE in cancer patients.<sup>121,122,123,241,246</sup>
- The use of extended low dose anticoagulation therapy for VTE has not been addressed fully in guidelines, as there is insufficient data to make firm recommendations at this time.
- Patient reported outcomes are notably absent in SVT treatment trials, and in pursuing the most cost-effective therapy, the end consumer (the patient) should not be ignored.
- While evidence exists that lower dose anticoagulants may effectively reduce VTE recurrence, the most effective therapy with the safest treatment profile and lowest cost is still being debated.

## **SUGGESTED RESEARCH TOPICS**

- Internationally recognized protocols for DVT and SVT ultrasound monitoring along time.
- Internationally recognized protocols for upper limb SVT management.
- Clinical trial enrolling high risk patients with differing treatment regimens for calf vein DVT.
- Glycosaminoglycans as an unexplored target in the vein wall and their potential benefits in reducing recurrent VTE and inflammation.

## **12. SCIENTIFIC WORK LIMITATIONS**

One of the main topics treated in this global analysis is the lower limb chronic venous disease (CVD) management. One of the most challenging issues is the report of the different international indications to CVD treatment. Indeed, not only significantly different indications are present, but also the same definition of “indication” and of “treatment” is lacking a proper globally accepted connotation.

Indeed, it should be specified if the indication is the one related to a governmental/insurance related scenario, or if it is related to the aim of a clinical result. Even more, it should be specified if the indication is strictly bond to a purely signs/symptoms associated clinical presentation, or if the aesthetic component can have a determinant role.

As reported by McKinlay, every nation can present significant variability in indication to treatment for whatever pathology, based not just on the economic organization of the same country, but also on patient and provider characteristics.<sup>335</sup>

The above described difficulty becomes particularly evident whenever considering that some nations are faster than other in adapting their health reimbursement plan based also on the most recent evidence based data: for example, venous active drugs can be reimbursed even in the milder disease stages in some countries, while not reimbursed in other countries even for the most severe clinical classes.<sup>336,337</sup>

A deep analysis of all the different countries reimbursement policies and scientific societies indication to treatment is above the scope of this scientific work.

Main endpoint of this international experts gathering and consensus has been to picture the current situation in terms of similarities and controversies in current global guidelines.

Following this first analysis, international venous and lymphatic societies are encouraged to foster a stronger inter-societies teamwork, so to promote more homogeneous guidelines, so leading also to more similar indications to treatment around the world.

A bias can be found in the selection of the same experts whenever dealing with guidelines, expert opinions and recommendations in general,.

Indeed, the same recommendations can be influenced by personal judgment and experience, as well as by geographical origin.<sup>338</sup>

In order to limit this last aspect, all the experts involved in the present work have curricula including major scientific roles in guidelines and scientific research on the specific working group topic they participated in.

In order to guarantee global representation, all the working groups had at least 5 experts each, coming from different continents.

All the continents enjoyed proper representation, except Africa. Unfortunately, apart a significantly top quality venous and lymphatic scientific level present in Egypt, grouped in two main societies, no other group of experts was found in the other African countries, despite the attempt done of reaching out to local doctors. Indeed, at the v-WINter congress, a project aimed to reach out more actively to African countries vein and lymphatic experts was proposed and is now in progress.

The narrative rather than systemic revision nature of the present work could be considered a potential limitation as well.

The reason of this methodology choice is to be found in the main endpoint of the same work, which is not to lead to a final recommendation based on the evidence-based data, rather to depict the current heterogeneity in the different recommendations from the different countries, and even from the same country different organizations.

Moreover, a narrative revision, compared to a systemic one, presents the advantage of reporting the insight of experts opinions, taking into account intuitive and experiential perspective, ultimately fueling future research direction.<sup>339</sup>

Indeed, the authors hope is that the present document can represent a starting point for future systemic revisions, leading to more homogeneous international guidelines.

The present work focused mainly on international societies recommendations rather than on governmental/insurance recommendations: indeed the aim remains a first “call to the scientific army” for evaluating the current controversies in global recommendations, so to set a ground zero from where building proper indications, involving subsequently also the policy makers and insurances delegates.

### **13. REFERENCES**

1. De Maeseneer M, Pichot O, Cavezzi A, et al. Duplex Ultrasound Investigation of the Veins of the Lower Limbs after Treatment for Varicose Veins – UIP Consensus Document. *Eur J Vasc Endovasc Surg.* 2011;42:89–102.

2. Gloviczki P, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: Clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J. Vasc Surg* 2011;53(5 Suppl):2S-48S.
3. Lurie F, Comerota A, Eklof B, et al. Multicenter assessment of venous reflux by duplex ultrasound. *J. Vasc Surg.* 2012;55:437–445.
4. 2014 American Vein & Lymphatic Society Practice Guidelines Duplex Ultrasound Imaging [http://www.phlebology.org/wpcontent/uploads/2014/11/ACP\\_Imaging\\_Guidelines\\_rev1109\\_a.pdf](http://www.phlebology.org/wpcontent/uploads/2014/11/ACP_Imaging_Guidelines_rev1109_a.pdf)
5. Capitulo Espanolo de Flebologia Y Linfologia - Guías de Práctica Clínica en Enfermedad Venosa Crónica [http://www.capitulodeflebologia.org/media/Guias-Practica-Clinica-Enfermedad-Venosa-Cronica\\_431.pdf](http://www.capitulodeflebologia.org/media/Guias-Practica-Clinica-Enfermedad-Venosa-Cronica_431.pdf)
6. Wittens C, Davies A, Bækgaard N, et al. Editors Choice – Management of Chronic Venous Disease. *Eur J Vasc Endovasc Surg*; 2015;49:678-737.
7. American Institute of Ultrasound in Medicine (AIUM) Practice Guideline for the Performance of Peripheral Venous Ultrasound 2015 Examinations. <https://www.aium.org/resources/guidelines/peripheralVenous.pdf>
8. Guías latinoamericanas de terapéutica para la patología venosa. Available at [http://www.capitulodeflebologia.org/media/Guias-Practica-Clinica-Enfermedad-Venosa-Cronica\\_431.pdf](http://www.capitulodeflebologia.org/media/Guias-Practica-Clinica-Enfermedad-Venosa-Cronica_431.pdf)
9. Lee D-K, Ahn K-S, Kang CH, et al. Ultrasonography of the lower extremity veins: anatomy and basic approach. *Ultrasonography.* 2017;36:120–130.
10. Spinedi L, Broz P, Engelberger RP, et al. Clinical and duplex ultrasound evaluation of lower extremities varicose veins – a practical guideline. *Vasa.*2017;46: 325–336.
11. Nicolaides A, Kakkos S, Bækgaard N, Comerota A, De Maeseneer M, Eklof B, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. *Int Angiol* 2018;37:181-254. DOI: 10.23736/S0392-9590.18.03999-8

12. 2018 IAC Standards and Guidelines for Vascular Testing Accreditation  
<https://www.intersocietal.org/vascular/standards/IACVascularTestingStandards2018.pdf>
13. Needleman L, Cronan JJ, Lilly MP, et al. Ultrasound for Lower Extremity Deep Venous Thrombosis. *Circulation*. 2018 ; 137: 1505–1515.
14. Masuda EM, Kistner RL, Musikasinthorn C, et al. The controversy of managing calf vein thrombosis. *J Vasc Surg*. 2012;55:550-61.
15. Palareti G. How I treat isolated distal deep vein thrombosis (IDDVT). *Blood*. 2014;123:1802–1809.
16. Righini M, Galanaud J-P, Guenneguez H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. *The Lancet Haematol*. 2016;3:e556-e562
17. Schellong SM. Low risk is not enough: the dilemma of calf vein thrombosis. *The Lancet Haematology*2016;3:e548-e549.
18. Kalodiki E, Stvrtinova V, Allegra C et al. Superficial vein thrombosis: a consensus statement. *Int Angiol* 2012;31:203-16
19. Barrellier MT. Superficial venous thromboses of the legs. *Phlébologie* 1993;46:633-9.
20. Sloves J, Almeida JJ. Venous duplex ultrasound protocol for ilio caval disease. *J Vasc Surg Venous Lymphat Disord*. 2018;6:748-757.
21. Labropoulos N, Jasinski PT, Adrahtas D, et al. A standardized ultrasound approach to pelvic congestion syndrome. *Phlebology*. 2017;32:608-619.
22. Hamel-Desnos CM, De Maeseneer M, Josnin M, et al. Great Saphenous Vein Diameters in Phlebological Practice in France: A Report of the DIAGRAVES Study by the French Society of Phlebology. *Eur J Vasc Endovasc Surg*. 2018. pii: S1078-5884(18)30684-1.
23. Giancesini S, Sisini F, Domenico GD, et al. Lower limbs venous kinetics and consequent impact on drainage direction. *Phlebology*. 2018; 33:107-114

24. Giancesini S, Menegatti E, Sisini F, et al. Comparison Between Duplex Ultrasound and Multigate Quality Doppler Profile Software in the Assessment of Lower Limb Perforating Vein Direction. *Eur J Vasc Endovasc Surg* 2018;55:688-693.
25. Bechsgaard T, Hansen K, Brandt A, et al. Evaluation of Peak Reflux Velocities with Vector Flow Imaging and Spectral Doppler Ultrasound in Varicose Veins. *Ultrasound Int Open*. 2018;4:E91-E98.
26. Metzger PB, Rossi FH, Kambara AM, et al. Criteria for detecting significant chronic iliac venous obstructions with duplex ultrasound. *J Vasc Surg Venous Lymphat Disord*. 2016;4: 18–27.
27. Raju S, Kirk O, Davis M, et al. Hemodynamics of “critical” venous stenosis and stent treatment. *J Vasc Surg Venous Lymphat Disord*.2014;2: 52–59.
28. Razavi M, Marston W, Black S, et al. The initial report on 1-year outcomes of the feasibility study of the VENITI VICI VENOUS STENT in symptomatic iliofemoral venous obstruction. *J Vasc Surg Venous Lymphat Disord*. 2018;6:192–200.
29. Rossi FH, Kambara AM, Izukawa NM, et al. Randomized double-blinded study comparing medical treatment versus iliac vein stenting in chronic venous disease. *J Vasc Surg Venous Lymphat Disord*.2018;6:183–191.
30. Gerhard-Herman M, Gardin JM, Jaff M, et al. Guidelines for noninvasive vascular laboratory testing: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. *Vasc Med*. 2006;11:183-200.
31. Raju S, Buck WJ, Crim W, et al. Optimal sizing of iliac vein stents. *Phlebology*. 2018; 33: 451–457.
32. Odonnell TF, Passman MA. Clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)--Management of venous leg ulcers. Introduction. *J Vasc Surg*. 2014;60(2 Suppl):1S-2S.
33. Giancesini S, Occhionorelli S, Menegatti E et al. CHIVA strategy in chronic venous disease treatment: instructions for users. *Phlebology*. 2015 Apr;30(3):157-71.
34. Cappelli M, Molino Lova R, Ermini S, Zamboni P. Hemodynamics of the sapheno-femoral junction. Patterns of reflux and their clinical implications. *Int Angiol* 2004; 23:25–28.

35. Cappelli M, Molino Lova R, Ermini S, Giangrandi I, Giannelli F, Zamboni P. Hemodynamics of the sapheno-femoral complex: an operational diagnosis of proximal femoral valve function. *Int Angiol* 2006; 25: 356–360.
36. Zamboni P, Giancesini S, Menegatti E, Tacconi G, Palazzo A, Liboni A. Great saphenous varicose vein surgery without saphenofemoral junction disconnection. *Br J Surg*. 2010 Jun;97(6):820-5.
37. Giancesini S, Occhionerelli S, Menegatti E, et al. Femoral vein valve incompetence as a risk factor for junctional recurrence. *Phlebology*. 2018;33:206-212.
38. Australasian college of phlebology guidelines. Diagnose venous disease and treat superficial venous incompetence with Endovenous Laser Ablation under Ultrasound Guidance. Available at [http://www.phlebology.com.au/file\\_uploads/9content2EVLAClinicalProceduresStandard2010.pdf](http://www.phlebology.com.au/file_uploads/9content2EVLAClinicalProceduresStandard2010.pdf)
39. Pavlović MD, Schuller-Petrović S, Pichot O, Rabe E, Maurins U, Morrison N, Pannier F. Guidelines of the First International Consensus Conference on Endovenous Thermal Ablation for Varicose Vein Disease--ETA V Consensus Meeting 2012. *Phlebology*. 2015;30:257-73.
40. Varicose veins in the legs. The diagnosis and management of varicose veins. Clinical guideline. Methods, evidence and recommendations. Commissioned by the National Institute for Health and Care Excellence. Available at <https://www.nice.org.uk/guidance/cg168/evidence/full-guideline-pdf-191485261>
41. Treatment of superficial venous disease of the lower leg. Guidelines of American Vein & Lymphatic Society (former American College of Phlebology). Available at <http://www.phlebology.org/wpcontent/uploads/2016/02/SuperficialVenousDiseaseGuidelinesPMS313-02.03.16.pdf>
42. Hamann SAS, Giang J, De Maeseneer MGR, et al. Editor's Choice – Five Year Results of Great Saphenous Vein Treatment: A Meta-analysis. *Eur J Vasc Endovasc Surg*. 2017 ;54:760-770.
43. Aurshina A, Ascher E, Victory J, et al. Clinical correlation of success and acute thrombotic complications of lower extremity endovenous thermal ablation. *J Vasc Surg Venous Lymphat Disord*. 2018 ;6:25-30.



44. Lawson JA, Gauw SA, van Vlijmen CJ, et al. Prospective comparative cohort study evaluating incompetent great saphenous vein closure using radiofrequency-powered segmental ablation or 1470-nm endovenous laser ablation with radial-tip fibers (Varico 2 study). *J Vasc Surg Venous Lymphat Disord*. 2018;6:31-40.
45. Belramman A, Bootun R, Lane TRA, et al. Endovenous Management of Varicose Veins. *Angiology*. 2018 Jan 1:3319718780049.
46. Gibson K1, Khilnani N2, Schul M3, et al. American College of Phlebology Guidelines - Treatment of refluxing accessory saphenous veins. *Phlebology*. 2017 Aug;32(7):448-452. doi: 10.1177/0268355516671624. Epub 2016 Oct 13.
47. Bozkurt AK, Yilmaz MF. A prospective comparison of a new cyanoacrylate glue and laser ablation for the treatment of venous insufficiency. *Phlebology*. 2016 Mar;31(1 Suppl):106-13.
48. Witte ME, Zeebregts CJ, de Borst GJ, et al. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: A systematic review. *Phlebology*. 2017;32:649-657.
49. Gibson K, Morrison N, Kolluri R et al. Twenty-four month results from a randomized trial of cyanoacrylate closure versus radiofrequency ablation for the treatment of incompetent great saphenous veins. *J Vasc Surg Venous Lymphat Disord*. 2018;6:606-613.
50. Holewijn S, van Eekeren RRJP, Vahl A, de Vries JPPM, Reijnen MMPJ; MARADONA study group. Two-year results of a multicenter randomized controlled trial comparing Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence (MARADONA trial). *J Vasc Surg Venous Lymphat Disord*. 2019 May;7(3):364-374.
51. Vähäaho S, Mahmoud O, Halmesmäki K, Albäck A, Noronen K, Vikatmaa P, Aho P, Venermo M. Randomized clinical trial of mechanochemical and endovenous thermal ablation of great saphenous varicose veins. *Br J Surg*. 2019 Apr;106(5):548-554.
52. Leung C, Carradice D, Mohamed A, et al. (abstract) A Randomized Controlled Trial Comparing Endovenous Laser Ablation vs Mechanochemical Ablation in the Treatment of Superficial Venous Incompetence: The LAMA Trial. *J Vasc Surg* 2017;65:S35

53. Hżeci M, Terlecki P, Przywara S, et al. A new device for minimally invasive mechano-chemical method of saphenous vein ablation. Report of 12 months of follow up. *Acta Angiologica* 2018; 24: 67-73.
54. Vos CG, Ünlü Ç, Bosma J et al. A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein. *J Vasc Surg Venous Lymphat Disord.* 2017;5:880-896.
55. Eroglu E, Yasim A. A Randomised Clinical Trial Comparing N-Butyl Cyanoacrylate, Radiofrequency Ablation and Endovenous Laser Ablation for the Treatment of Superficial Venous Incompetence: Two Year Follow up Results. *Eur J Vasc Endovasc Surg.* 2018;56:553-560.
56. Obi AT, Reames BN, Rook TJ et al. Outcomes associated with ablation compared to combined ablation and transilluminated powered phlebectomy in the treatment of venous varicosities. *Phlebology.* 2016;31:618-24.
57. Hager ES, Ozvath KJ, Dillavou ED. Evidence summary of combined saphenous ablation and treatment of varicosities versus staged phlebectomy. *J Vasc Surg Venous Lymphat Disord.* 2017;5:134-137.
58. Sutzko DC, Andraska EA, Obi AT. Age is not a barrier to good outcomes after varicose vein procedures. *J Vasc Surg Venous Lymphat Disord.* 2017;5:647-657.e1
59. Çalık ES, Arslan Ü, Erkut B. Ablation therapy with cyanoacrylate glue and laser for refluxing great saphenous veins - a prospective randomised study. *Vasa.* 2019 Apr 24:1-8.
60. Yang GK, Parapini M, Gagnon J, Chen JC. Comparison of cyanoacrylate embolization and radiofrequency ablation for the treatment of varicose veins. *Phlebology.* 2019 May;34(4):278-283.
61. Sufian S, Arnez A, Labropoulos N, et al. Incidence, progression, and risk factors for endovenous heat-induced thrombosis after radiofrequency ablation. *J Vasc Surg Venous Lymphat Disord.* 2013;1:159-64.
62. Sufian S, Arnez A, Labropoulos N, et al. Endothermal venous ablation of the saphenous vein on patients who are on anticoagulation therapy. *Int Angiol.* 2017;36:268-274.
63. Nyamekye IK. Effective anti-DVT prophylaxis in patients undergoing endovenous treatment of varicose veins. *Phlebology.* 2018;33:68-69.

64. Sweetland S, Green J, Liu B. Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ*. 2009;3;339:b4583.
65. Goodyear SJ and Nyamekye I. Rational anti-DVT prophylaxis for ambulatory varicose veins procedures. In: Greenhalge RM (ed.) *Vascular and endovascular challenges update*. London: BIBA Publishing, 2016, pp.541–549).
66. Shaidakov EV, Grigoryan AG, Ilyukhin A, et al. Radiofrequency ablation or stripping of large-diameter incompetent great saphenous varicose veins with C2 or C3 disease. *J Vasc Surg Venous Lymphat Disord*. 2016; 4: 45-50.
67. Shaydakov EV, Ilyukhin E, Rosukhovskiy D. Blood absorption during 970 and 1470 nm laser radiation in vitro. *Int Angiol*. 2015; 34: 475-482.
68. Shaydakov EV, Grigoryan AG, Korzhevskii D, et al. Morphologic changes in the vein after different numbers of radiofrequency ablation cycles. *J Vasc Surg Venous Lymphat Disord*. 2015; 4: 358-363
69. Shaidakov EV, Grigorian AG, Bulatov V, et al. Results of Great Saphenous Vein Endovenous Laser Ablation with a Wavelength of 1470 nm Using Radial 2ring Fiber With Different Linear Energy Density. *J Vasc Surg Venous Lymphat Disord*. 2017;5:151.
70. Spreafico G, Giordano R, Piccioli A, Iaderosa G, Pavei P, Giraldi E, et al. Histological damage of saphenous venous wall treated in vivo with radial fiber and 1470 nm diode laser. *Italian J Vasc Endovasc Surg* 2011;18:241-7
71. T. Yamamoto and M. Sakata. Influence of fibers and wavelengths on the mechanism of action of endovenous laser ablation. *J Vasc Surg: venous and lymphatic disorders*, January 2014
72. Sergio GIANESINI, Roberta GAFÀ, Savino OCCHIONORELLI, et al. Histologic and sonographic features of holmium laser in the treatment of chronic venous disease. *International Angiology* 2017 April;36(2):122-8
73. Epstein D, Onida S, Bootun R, et al. Cost-Effectiveness of Current and Emerging Treatments of Varicose Veins. *Value Health*. 2018;21:911-920.

74. Epstein D, Gohel M, Heatley F, et al. Cost-effectiveness of treatments for superficial venous reflux in patients with chronic venous ulceration. *BJS Open*. 2018;10;2:203-212.
75. Tan M, Onida S, Davies AH. Quality of life tools reflect disease severity but can they be improved? *Phlebology*. 2018 Dec 4:268355518816573. [Epub ahead of print]
76. Giancesini S, Occhionerelli S, Menegatti E, et al. Femoral vein valve incompetence as a risk factor for junctional recurrence. *Phlebology*. 2018;33:206-212.
77. Tiwari A, Chong TT, Walsh SR, et al. Reporting outcomes of new and old endovenous technologies using a standardized dataset - Now is the time for change. *Phlebology*. 2019;34:5-7.
78. Ebner H, Stillo F, Lanza G et al. Linee guida flebo-linfologiche SIF-SICVE 2016 della Societa Italiana di Flebologia e della Societa Italiana di Chirurgia Vascolare ed Endovascolare. *Minerva cardioangiologica*. *Minerva Cardioangiol*. 2016;64:1-80.
79. NICE Coban 2 for venous leg ulcer. 2018 <https://www.nice.org.uk/advice/mib140/chapter/The-technology>
80. Rabe E, Partsch H, Hafner J, et al. Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. *Phlebology* 2018; 33:163–184.
81. Schwahn-Schreiber C, Breu FX, Rabe E, et al. Guidelines on intermittent pneumatic compression (IPC). *Hautarzt*. 2018;69:662-673.
82. Lurie F, Lal B, Antignani PL, et al. Compression therapy after invasive treatment of superficial veins of the lower extremities: Clinical practice guidelines of the American Venous Forum, Society for Vascular Surgery, American College of Phlebology, Society for Vascular Medicine, and International Union of Phlebology. *J Vasc Surg Venous Lymphat Disord* 2019;7:17-28
83. The Juxta CURES adjustable compression system for treating venous leg ulcers [nice.org.uk/guidance/mib25](https://www.nice.org.uk/guidance/mib25)
84. NHS Wound Management Guide: intermittent pneumatic compression. <https://www.covwarkpt.nhs.uk/download.cfm?doc=docm93jjm4n2740.pdf&ver=3517>.

85. Lee BY, Butler G, Al-Waili N, et al. Role of thrombelastograph haemostasis analyser in detection of hypercoagulability following surgery with and without use of intermittent pneumatic compression. *J Med Eng Technol.* 2010, 34:166-71
86. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e195S–226.
87. Mosti G, Cavezzi A. Compression therapy in lymphedema: Between past and recent scientific data. *Phlebology.* 2019; Jan 9:268355518824524. [Epub ahead of print]
88. Partsch H, Damstra RJ and Mosti G. Dose finding for an optimal compression pressure to reduce chronic edema of the extremities. *Int Angiol* 2011; 30: 527–533.
89. Damstra RJ, Brouwer ER, Partsch H. Controlled, comparative study of relation between volume changes and interface pressure under short-stretch bandages in leg lymphedema patients. *Dermatol Surg.* 2008;34:773-8.
90. Mosti G, Cavezzi A, Partsch H, et al. Adjustable Velcro Compression Devices are More Effective than Inelastic Bandages in Reducing Venous Edema in the Initial Treatment Phase: A Randomized Controlled Trial. *Eur J Vasc Endovasc Surg.* 2015;50:368-74.
91. Damstra RJ, Partsch H. Prospective, randomized, controlled trial comparing the effectiveness of adjustable compression Velcro wraps versus inelastic multicomponent compression bandages in the initial treatment of leg lymphedema. *J Vasc Surg Venous Lymphat Disord.* 2013;1:13-9.
92. Mosti G, Picerni P and Partsch H. Compression stockings with moderate pressure are able to reduce chronic leg oedema. *Phlebology* 2012; 27: 289–296.
93. Mosti G and Partsch H. Bandages or double stockings for the initial therapy of venous oedema? A randomized, controlled pilot study. *Eur J Vasc Endovasc Surg* 2013; 46: 142–148.
94. Mosti G, Iabichella ML and Partsch H. Compression therapy in mixed ulcers increases venous output and arterial perfusion. *J Vasc Surg* 2012; 55: 122–128.

95. Stansal A, Tella E, Yannoutsos A, et al. Supervised short-stretch compression therapy in mixed leg ulcers. *J Med Vasc*. 2018;43:225-230.
96. De Carvalho MR, Peixoto BU, Silveira IA, et al. A Meta-analysis to Compare Four-layer to Short-stretch Compression Bandaging for Venous Leg Ulcer Healing. *Ostomy Wound Manage*. 2018;64:30-37.
97. O'Meara S, Cullum N, Nelson EA, et al. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2012; 11:CD000265.
98. Partsch H and Mortimer P. Compression for leg wounds. *Br J Dermatol* 2015;173:359-369
99. Blecken S, Villavicencio J, Kao T. Comparison of elastic versus nonelastic compression in bilateral venous ulcers: A randomized trial. *J Vasc Surg* 2005;42:1150 –5.
100. Benigni JP, Uhl JF, Balet F, et al. Evaluation of three different devices to reduce stasis edema in poorly mobile nursing home patients. *Int Angiol*. 2018;37:322-326.
101. Pujol-Blaya V, Salinas-Huertas S, Catasús ML, et al. Effectiveness of a precast adjustable compression system compared to multi-layered compression bandages in the treatment of breast cancer-related lymphoedema: a randomized, single-blind clinical trial. *Clin Rehabil*. 2019;33:631-641.
102. Tiwari A, Cheng KS, Button M, et al. Differential diagnosis, investigation, and current treatment of lower limb lymphedema. *Arch Surg*. 2003;138:152-61.
103. Zaki M, Elsherif M, Tawfick W, et al. The Role of Sequential Pneumatic Compression in Limb Salvage in Non-reconstructable Critical Limb Ischemia. *Eur J Vasc Endovasc Surg* 2016;51:565-571.
104. Alvarez OM, Wendelken ME, Markowitz L, et al. Effect of high-pressure intermittent pneumatic compression for the treatment of peripheral arterial disease and critical limb ischemia in patients without a surgical option. *Wounds* 2015;27: 293–301.
105. Nandwana S, Ho K. A comparison of different modes of pneumatic compression on muscle tissue oxygenation: An intraparticipant, randomised, controlled volunteer study. *Anaesthesia and Intensive Care* 2019;47:23–31.

106. Kakkos SK, Caprini JA, Geroulakos G, et al. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev.* 2016;9:CD005258:CD005258.
107. Arabi YM, Al-Hameed F, Burns KEA et al. Adjunctive Intermittent Pneumatic Compression for Venous Thromboprophylaxis. *N Engl J Med.* 2019;380:1305-1315.
108. Biswas S, Clark A, Shields DA, et al. Randomised clinical trial of the duration of compression therapy after varicose vein surgery. *Eur J Vasc Endovasc Surg.* 2007;33:631-7.
109. Hamel-Desnos CM, Guias BJ, Desnos PR, et al. Foam sclerotherapy of the saphenous veins: randomised controlled trial with or without compression. *Eur J Vasc Endovasc Surg.* 2010;39:500-7.
110. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet.* 2014;383:880-8.
111. Labropoulos N, Gasparis AP, Caprini JA, et al. Compression stockings to prevent post-thrombotic syndrome. *Lancet.* 2014;384:129-30.
112. Mosti G, Mattaliano V, Partsch H. Influence of different materials in multicomponent bandages on pressure and stiffness of the final bandage. *Dermatol Surg.* 2008;34:631-9.
113. Mosti G, De Maeseneer M, Cavezzi A, et al. 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. *Int Ang* 2015;34:202-18
114. Partsch H, Clark M, Mosti G, et al. Classification of compression bandages: practical aspects. *Dermatol Surg.* 2008;34:600-609.
115. Cornwell EE, 3rd, Chang D, Velmahos G, et al. Compliance with sequential compression device prophylaxis in at-risk trauma patients: a prospective analysis. *Am Surg.* 2002;68:470-473.
116. Maxwell GL, Synan I, Hayes RP, Clarke-Pearson DL. Preference and compliance in postoperative thromboembolism prophylaxis among gynecologic oncology patients. *Obstet Gynecol.* 2002;100:451-455.

117. Wicks, G. An alternative to compression bandaging in venous leg ulcers. *Journal of Community Nursing* 2015; 29:40–46.
118. Williams A. A review of the evidence for adjustable compression wrap devices. *J Wound Care*. 2016;25:242-7. Review.
119. MedStar Health policy and procedure manual  
[https://www.medstarprovidernetwork.org/sites/default/files/attachments/Varicose%20Veins%20MP.066.MH\\_.pdf](https://www.medstarprovidernetwork.org/sites/default/files/attachments/Varicose%20Veins%20MP.066.MH_.pdf).
120. NICE 2018 <http://pathways.nice.org.uk/pathways/venous-thromboembolism>.
121. Liew NC, Alemany GV, Angchaisuksiri P, et al. Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism. *Int Angiol*. 2017;36:1-20.
122. Kearon C, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315-352.
123. Excellence (NICE). Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. Clinical guideline [CG144]: published June 2012, updated November 2015.
124. Malaysian Clinical practice guidelines: prevention and treatment of venous thromboembolism. 2013  
<http://www.moh.gov.my/penerbitan/CPG2017/9005.pdf>
125. Vascular Surgery. Guidelines deep venous thrombosis; 2015. Available from: [www.anzsvs.org.au](http://www.anzsvs.org.au).
126. Wissenschaftlichen Medizinischen Fachgesellschaften e.V. S2-Leitlinie: Diagnostik und Therapie der Venenthrombose und der Lungenembolie. AWMF Leitlinien- Register Nr. 065/002; 2015.
127. Haute Autorité de Santé (HAS). La compression médicale dans le traitement de la maladie thromboembolique veineuse; Décembre 2010.
128. NHG-werkgroep diepe veneuze trombose en longembolie. NHG Standaard: diepe veneuze trombose en longembolie. *Huisarts Wet* 2015;58:26-35.
129. Watson HG, Baglin TP. Guidelines on travel-related venous thrombosis. *Br J Haematol*. 2011;152:31-4.



130. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Royal College of Obstetricians & Gynaecologists 2015. <https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf>
131. Kakkos SK, Timpilis M, Patrinos P, et al. Acute Effects of Graduated Elastic Compression Stockings in Patients with Symptomatic Varicose Veins: A Randomised Double Blind Placebo Controlled Trial. *Eur J Vasc Endovasc Surg.* 2018;55:118-125.
132. Amsler F, Rabe E, Blättler W. Leg symptoms of somatic, psychic, and unexplained origin in the population based Bonn Vein Study. *Eur J Vasc Endovasc Surg* 2013;46:255-62.
133. Castilho Junior OT, Dezotti NRA, Dalio MB, et al. Effect of graduated compression stockings on venous lower limb hemodynamics in healthy amateur runners. *J Vasc Surg Venous Lymphat Disord.* 2018;6:83-89.
134. Giancesini S, Tessari M, Menegatti E, et al. Comparison between the effects of 18- and 23-mmHg elastic stockings on leg volume and fatigue in golfers. *Int Angiol.* 2017;36:129-135.
135. Giancesini S, Raffetto J, Mosti G, et al. Graduated Compression Lower Limb Volume Control in Different Muscle Pump Activation Conditions and Related Limb Shape Impact. *J Vasc Surg Venous Lymphat Disord.* 2019;7:295-6.
136. Ashby RL, Gabe R, Ali S, et al. Clinical and cost-effectiveness of compression hosiery versus compression bandages in treatment of venous leg ulcers (Venous leg Ulcer Study IV, VenUS IV): a randomised controlled trial. *Lancet.* 2014;383:871-9.
137. Hobson DB, Chang TY, Aboagye JK, et al. Prevalence of graduated compression stocking-associated pressure injuries in surgical intensive care units. *J Crit Care.* 2017;40:1-6.
138. Zha ML, Chen HL. A specific risk assessment scale for GCS-associated pressure ulcer should be established and used before using graduated compression stocking. *J Crit Care.* 2017;40:286
139. Cavalcante BR, Ritti-Dias RM, Germano Soares AH, et al. Graduated Compression Stockings Does Not Decrease Walking Capacity and Muscle Oxygen Saturation during 6-Minute Walk Test in Intermittent Claudication Patients. *Ann Vasc Surg.* 2017;40:239-242.

140. Sachdeva A, Dalton M, Lees T. et al. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2018;11:CD001484.
141. Afshari A, Fenger-Eriksen C, Monreal M, et al. European guidelines on perioperative venous thromboembolism prophylaxis: Mechanical prophylaxis. *Eur J Anaesthesiol*. 2018;35:112-115
142. Amin EE, Bistervels IM, Meijer K et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. *Blood*. 2018 Nov 22;132:2298-2304.
143. Tie HT, Luo MZ, Luo MJ, et al. Compression therapy in the prevention of postthrombotic syndrome: a systematic review and meta-analysis. *Medicine* 2015;94:1-8.
144. Jin YW, Ye H, Li FY, et al. Compression stockings for prevention of postthrombotic syndrome: a systematic review and meta-analysis. *Vasc Endovasc Surg* 2016;50:328-34.
145. Subbiah R, Aggarwal V, Zhao H, et al. Effect of compression stockings on post-thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. *Lancet Haematol* 2016;3:293-300.
146. Burgstaller JM, Steurer J, Held U, Amann-Vesti B. Efficacy of compression stockings in preventing post-thrombotic syndrome in patients with deep venous thrombosis: a systematic review and metaanalysis. *Vasa* 2016;45:141-7.
147. Appelen D, van Loo E, Prins MH, et al. Compression therapy for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* 2017;9:CD004174.
148. Ten Cate-Hoek AJ, Amin EE, Bouman AC, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol*. 2018;5:e25-e33.
149. Al Shakarchi J, Wall M, Newman J, et al. The role of compression after endovenous ablation of varicose veins. *J Vasc Surg Venous Lymphat Disord*. 2018;6:546-550.

150. Cavezzi A, Mosti G, Colucci R, et al. Compression with 23 mmHg or 35 mmHg stockings after saphenous catheter foam sclerotherapy and phlebectomy of varicose veins: A randomized controlled study. *Phlebology*. 2019;34:98-106.
151. Horiuchi M, Takiguchi C, Kirihara Y. Impact of Wearing Graduated Compression Stockings on Psychological and Physiological Responses during Prolonged Sitting. *Int J Environ Res Public Health*. 2018;10;15: pii: E1710.
152. Sénat MV, Sentilhes L, Battut A, et al. Postpartum practice: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol*. 2016 Jul;202:1-8.
153. Peyronnet V, Roses A, Girault A, et al. Lower limbs venous compression reduces the incidence of maternal hypotension following epidural analgesia during term labor. *Eur J Obstet Gynecol Reprod Biol*. 2017 ;219:94-99.
154. Merriam AA, Huang Y, Ananth CV et al. Postpartum Thromboembolism Prophylaxis during Delivery Hospitalizations. *Am J Perinatol*. 2018;35:873-881.
155. Chau C, Campagna J, Vial M, et al. Use of a personalized iterative score to evaluate risk of venous thromboembolism during pregnancy and puerperium. *Int J Gynaecol Obstet*. 2019;144:277-282.
156. Becher K, Abraham S. Pain management and wound care. *J Am Col Certif Wound Spec*. 2009;1:65–71.
157. NICE 2013 <https://www.nice.org.uk/researchrecommendation/compression-after-interventional-treatment-what-is-the-clinical-and-cost-effectiveness-of-compression-bandaging-or-hosiery-after-interventional-treatment-for-varicose-veins-compared-with-no-compression-if-there-is-benefit-how-long-should-compression-banda>.
158. Clarke MJ, Broderick C, Hopewell S, et al. Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Syst Rev*. 2016;9:CD004002.
159. Sultan AA, West J, Tata LJ, et al. Risk of first venous thromboembolism in and around pregnancy: a population-based cohort study. *Br J Haematol*. 2012;156:366- 373.

160. Heit JA. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med.* 2005;143:697-706.
161. Catherine C. Physiologic changes of pregnancy: A review of the literature. *Int J Womens Dermatol.* 2017; 3: 219–224.
162. Jamieson R. The effect of graduated compression stockings on blood velocity in the deep venous system of the lower limb in the postnatal period. *BJOG.* 2007;114:1292-4.
163. Dennis M, Sandercock PA, Reid J, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. *Lancet.* 2009;373:1958-65.
164. Dennis M, Cranswick G, Deary A, et al. Thigh-Length Versus Below-Knee Stockings for Deep Venous Thrombosis Prophylaxis After Stroke. *Ann Intern Med.* 2010;153:553-62.
165. Dennis M, Cranswick G, Deary A et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet* 2013, 382: 516–24
166. Khunger N, Sacchidanand S. Standard Guidelines for care: Sclerotherapy in dermatology. *Indian J Dermatol Venereol Leprol.* 2011; 77: 222-31.
167. Rathbun S, Norris A, Morrison N, et al. Performance of endovenous foam sclerotherapy in the USA for the treatment of venous disorders: ACP\*/SVM/AVF/SIR quality improvement guidelines. *Phlebology.* 2014;29:76-82.
168. Weiss M, Hsu J, Neuhaus I, et al. Consensus for sclerotherapy. American Society for Dermatologic Surgery. *Dermatol Surg* 2014;40:1309–1318
169. Rabe E, Breu FX, Cavezzi A, et al. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology.* 2014;29:338-54.
170. Australasian College of Phlebology. Diagnose venous disease and treat superficial venous incompetence with injected sclerosants under ultrasound guidance. 2016 ACP Standards Guidelines. Available in: <http://www.phlebology.com.au/standards>.

171. Australasian College of Phlebology. Assess and treat abnormal superficial venous network with injected sclerosants. 2016 ACP Standards Guidelines. Available in: <http://www.phlebology.com.au/standards>.
172. Davies HO, Popplewell M, Darvall K, et al. A review of randomised controlled trials comparing ultrasound-guided foam sclerotherapy with endothermal ablation for the treatment of great saphenous varicose veins. *Phlebology*. 2016 May;31(4):234-40.
173. Vähäaho S, Halmesmäki K, Albäck A et al. Five-year follow-up of a randomized clinical trial comparing open surgery, foam sclerotherapy and endovenous laser ablation for great saphenous varicose veins. *Br J Surg*. 2018;105:686-691.
174. Lawaetz M, Serup J, Lawaetz B, et al. Comparison of endovenous ablation techniques, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Extended 5-year follow-up of a RCT. *Int Angiol*. 2017;36:281-288.
175. Lam YL, Lawson JA, Toonder IM, et al. Eight-year follow-up of a randomized clinical trial comparing ultrasound-guided foam sclerotherapy with surgical stripping of the great saphenous vein. *Br J Surg*. 2018;105:692-698.
176. Kalodiki E, Azzam M, Schnatterbeck P, et al. The Discord Outcome Analysis (DOA) as a Reporting Standard at Three Months and Five Years in Randomised Varicose Vein Treatment Trials. *Eur J Vasc Endovasc Surg*. 2019;57:267-274.
177. Bai T, Jiang W, Chen Y, et al. Effect of Multiple Factors on Foam Stability in Foam Sclerotherapy. *Sci Rep*. 2018;8:15683.
178. Critello CD, Fiorillo AS, Cristiano MC et al. Effects of sulodexide on stability of sclerosing foams. *Phlebology*. 2019;34:191-200.
179. Star P, Connor DE, Parsi K. Novel developments in foam sclerotherapy: Focus on Varithena (polidocanol endovenous microfoam) in the management of varicose veins. *Phlebology*. 2018;33:150-162.

180. Kolluri R, Hays KU, Gohel MS, et al. Foam Sclerotherapy Augmented Phlebectomy (SAP) Procedure for Varicose Veins: Report of a Novel Technique. *EJVES Short Rep.* 2018 Nov 16;41:16-18.
181. (Cavezzi A, Mosti G, Campana F, et al. Catheter Foam Sclerotherapy of the Great Saphenous Vein, with Perisaphenous Tumescence Infiltration and Saphenous Irrigation *Eur J Vasc Endovasc Surg.* 2017;54:629-635.
182. Ali H, Elbadawy A, Saleh M, et al. Mid-term Results of Catheter Directed Foam Sclerotherapy Combined with Tumescence Local Anaesthesia for Treatment of Great Saphenous Vein Incompetence. *Eur J Vasc Endovasc Surg.* 2017;54:363-368.
183. Giancesini S, Menegatti E, Sibilla MG, et al. Mini-invasive foam sclerotherapy-assisted ligation versus surgical flush ligation for incompetent sapheno-popliteal junction treatment. *Phlebology.* 2019 Feb 26:268355519833229. [Epub ahead of print]
184. MacArthur CJ, Nesbit G. Simultaneous intra-operative sclerotherapy and surgical resection of cervicofacial venous malformations. *Int J Pediatr Otorhinolaryngol.* 2019;118:143-146.
185. Myers K. A history of injection treatments - II sclerotherapy. *Phlebology.* 2018 Oct 18:268355518798283. [Epub ahead of print]
186. Foam Sclerotherapy for Treatment of Varicose Veins: A Review of the Clinical Effectiveness, Safety, Cost-Effectiveness, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Feb. CADTH Rapid Response Reports.
187. Jia X, Mowatt G, Ho V, et al. J. Systematic review of the safety and efficacy of foam sclerotherapy for venous disease of the lower limbs . Aberdeen: University of Aberdeen, Health Services Research Unit . ReBIP Report. 2006.
188. Rathbun S, Norris A, Morrison N, et.al. Performance of endovenous foam sclerotherapy in the USA. *Phlebology.* 2012;27:59-66.
189. Raymond-Martimbeau P. Transient adverse events positively associated with patent foramen ovale after ultrasound-guided foam sclerotherapy. *Phlebology.* 2009;24:114-9.

190. Watkins MR. Deactivation of sodium tetradecyl sulphate injection by blood proteins. *Eur J Vasc Endovasc Surg.* 2011;41:521-5.
191. Morrison N, Neuhardt DL, Rogers CR, et al. Incidence of side effects using carbon dioxide-oxygen foam for chemical ablation of superficial veins of the lower extremity. *Eur J Vasc Endovasc Surg.* 2010;40:407-13.
192. Peterson JD, Goldman MP. An investigation of side-effects and efficacy of foam-based sclerotherapy with carbon dioxide or room air in the treatment of reticular leg veins: a pilot study. *Phlebology.* 2012;27:73-6.
193. Wong M. Should foam made with physiologic gases be the standard in sclerotherapy? *Phlebology* 2015;30:580–86.
194. Frullini A, Felice F, Burchielli S, et al. High production of endothelin after foam sclerotherapy: a new pathogenetic hypothesis for neurological and visual disturbances after sclerotherapy. *Phlebology.* 2011;26:203-8.
195. Kendler M, Kratzsch J, Schmidt R et al. Serum endothelin 1 levels before, during and after mechanochemical endovenous ablation with foam and surgical correction of incompetent great saphenous veins. *J Eur Acad Dermatol Venereol.* 2016;30:546-7.
196. Whiteley MS, Dos Santos SJ, Lee CT, et al. Mechanochemical ablation causes endothelial and medial damage to the vein wall resulting in deeper penetration of sclerosant compared with sclerotherapy alone in extrafascial great saphenous vein using an ex vivo model. *J Vasc Surg Venous Lymphat Disord.* 2017;5:370-77.
197. Adamič M, Pavlovic M, Troilius A, et al. Guidelines of care for vascular lasers and intense pulse light sources from the European Society for Laser Dermatology. *J Eur Acad Dermatol Venereol.* 2015;29:1661-78.
198. Meesters AA, Pitassi LH, Campos V, et al. Transcutaneous laser treatment of leg veins. *Lasers Med Sci.* 2014;29:481-92.

199. Goldman MP, Eckhouse S. Photothermal sclerosis of leg veins. ESC Medical Systems, LTD Photoderm VL Cooperative Study Group. *Dermatol Surg.* 1996;22:323–30.
200. McCoppin HH, Hovenic WW, Wheeland RG. Laser treatment of superficial leg veins: a review. *Dermatol Surg.* 2011;37:729–41.
201. Sadick NS. Laser treatment with a 1064-nm laser for lower extremity class I–III veins employing variable spots and pulse width parameters. *Dermatol Surg.* 2003 29:916–19.
202. Mordon S, Brisot D, Fournier N. Using a "non uniform pulse sequence" can improve selective coagulation with a Nd:YAG laser. *Lasers Surg Med.* 2003;32:160-70.
203. Bertanha M, Jaldin RG, Moura R et al. Sclerotherapy for Reticular Veins in the Lower Limbs: A Triple-Blind Randomized Clinical Trial. *JAMA Dermatol.* 2017;153:1249-255.
204. Bush R, Bush P. Evaluation of sodium tetradecyl sulfate and polidocanol as sclerosants for leg telangiectasia based on histological evaluation with clinical correlation. *Phlebology.* 2017;32:496-500
205. Kadam P, Lim J, Paver I, et al. Telangiectatic Matting is Associated with Hypersensitivity and a Bleeding Tendency. *Eur J Vasc Endovasc Surg.* 2018;55:554-59.
206. Moreno-Moraga J1, Pascu ML, Alcolea JM. Effects of 1064-nm Nd:YAG long-pulse laser on polidocanol microfoam injected for varicose vein treatment: a controlled observational study of 404 legs, after 5-year-long treatment. *Lasers Med Sci.* 2019 Feb 1. doi: 10.1007/s10103-019-02736-1. [Epub ahead of print]
207. Ianosi G, Ianosi S, Calbureanu-Popescu MX. Comparative study in leg telangiectasias treatment with Nd:YAG laser and sclerotherapy. *Exp Ther Med.* 2019;17:1106-112.
208. Crippa A, Menegatti E, Zini F, et al. Safety and short-term efficacy of telangiectasia treatment by means of an innovative combination of 532 and 808 nm transdermal diode laser. *Phlebology.* 2019 Apr 6:268355519841999. doi: 10.1177/0268355519841999. [Epub ahead of print]
209. Ruckley CV, Evans CJ, Allan PL et al. Telangiectasia in the Edinburgh Vein Study: epidemiology and association with trunk varices and symptoms. *Eur J Vasc Endovasc Surg.* 2008;36:719-24



210. Schuller-Petrović S, Pavlović MD, Schuller S, et al. Telangiectasias resistant to sclerotherapy are commonly connected to a perforating vessel. *Phlebology*. 2013;28:320-23.
211. Santiago FR, Piscocoya M, Chi YW. A sonographic study of thigh telangiectasias. *Phlebology*. 2018;33:500-01.
212. Ouvry P. Le teleangectasie degli arti inferiori. In: Bassi G. editor. *Compendio di terapia flebologica*. Turin: Minerva Medica 1985;105- 10.
213. Redisch W, Pelzer RH. Localized vascular dilatations of the human skin: capillary microscopy and related studies. *Am Heart J* 1949;37:106.
214. Damia S, Scicchitano G, Falappa PG, Camilli S. La microphlebographie des microvarices. *Phlebologie* 1994; 47:341-4.
215. Bohler-SommereggerK, Kamel F, Schuller-Petrovic S, Santler R. Do telangiectases communicate with the deep venous system? *J Dermatol Surg Oncol* 1992;18:403-6.
216. Somjen GM, Ziegenbein R, Johnston AH, Royle JP. Anatomical examination of leg telangiectases with duplex scanning. *J Dermatol Surg Oncol* 1993;19:940-5.
217. Somjen GM. Anatomy of the superficial venous system. *Dermatol Surg* 1995;21:35-45.
218. Weiss RA, Weiss MA. Doppler ultrasound findings in reticular veins of the thigh subdermic lateral venous system and implications for sclerotherapy. *J Dermatol Surg Oncol* 1993;19:947-51.
219. Weiss RA, Weiss MA. Continuous wave venous doppler examination for pretreatment diagnosis of varicose and telangiectactic veins. *Dermatol Surg* 1995;21 :58-62.
220. Ruckley CV1, Evans CJ, Allan PL, Lee AJ, Fowkes FG. Telangiectasia in the Edinburgh Vein Study: epidemiology and association with trunk varices and symptoms. *Eur J Vasc Endovasc Surg*. 2008 Dec;36(6):719-24
221. Mariani F, Bianchi, V, Mancini S, Mancini S. Telangiectases in Venous Insufficiency: Point of Reflux and Treatment Strategy. *Phlebology* 2000;15:38-42
222. Cappelli M. Riflessioni di Emodinamica sulle Teleangectasie. In: *Scleroterapia*, II ed (F. Mariani, S. Mancini); Edizioni Minerva Medica, Torino, 2006.

223. Tisi PV, Beverley C, Rees A. Injection sclerotherapy for varicose veins. *Cochrane Database Syst Rev*. 2006:CD001732. Review.
224. Lupton JR, Alster TS, Romero P. Clinical comparison of sclerotherapy versus long-pulsed Nd:YAG laser treatment for lower extremity telangiectases. *Dermatol Surg*. 2002;28:694-97
225. Munia MA, Wolosker N, Munia CG et al. Comparison of laser versus sclerotherapy in the treatment of lower extremity telangiectases: a prospective study. *Dermatol Surg*. 2012;38:635–39
226. Levy JL, Elbahr C, Jouve E et al. Comparison and sequential study of long pulsed Nd:YAG 1,064 nm laser and sclerotherapy in leg telangiectasias treatment. *Lasers Surg Med* 2014;34:273-76
227. Coles CM, Werner RS, Zelickson BD. Comparative pilot study evaluating the treatment of leg veins with a long pulse ND:YAG laser and sclerotherapy. *Lasers Surg Med*. 2002;30:154–59.
228. Schwartz L, Maxwell H. Sclerotherapy for lower limb telangiectasias. *Cochrane Database Syst Rev* 2011:CD008826.
229. Moreno-Moraga J, Hernandez E, Royo J et al Optimal and safe treatment of spider leg veins measuring less than 1.5 mm on skin type IV patients, using repeated low-fluence Nd:YAG laser pulses after polidocanol injection. *Lasers Med Sci*. 2013;28:925–33.
230. Goldman MP, Fitzpatrick RE. Pulsed-dye laser treatment of leg telangiectasia: with and without simultaneous sclerotherapy. *J Dermatol Surg Oncol* 1990;16:338–44.
231. Sadick NS, Trelles MA. A clinical, histological, and computer- based assessment of the Polaris LV, combination diode, and radiofre- quency system, for leg vein treatment. *Lasers Surg Med*. 2005;36:98–104.
232. Trelles MA, Martin-Vazquez M, Trelles OR et al (2006) Treatment effects of combined radio- frequency current and a 900 nm diode laser on leg blood vessels. *Lasers Surg Med* 38:185–95.
233. Shafirstein G, Moreno M, Klein A et al. Treatment of leg veins with indocyanine green and lasers investigated with mathematical modelling. *Int J Hyperthermia*. 2011;7:771–81.

234. Klein A, Baumler W, Koller M et al. Indocyanine green- augmented diode laser therapy of telangiectatic leg veins: a randomized controlled proof-of-concept trial. *Lasers Surg Med* 2012;44:369–76.
235. Klein A, Buschmann M, Babilas P, et al. Indocyanine green- augmented diode laser therapy vs. long-pulsed Nd:YAG (1064 nm) laser treatment of telangiectatic leg veins: a randomized controlled trial. *Br J Dermatol* 2013;169:365–73.
236. Tremaine AM, Friedmann DP, Goldman MP. Foam sclerotherapy for reticular veins of the dorsal hands: a retrospective review. *Dermatol Surg*. 2014;40:892-8.
237. Jia W, Tran N, Sun V et al. Photocoagulation of dermal blood vessels with multiple laser pulses in an in vivo microvascular model. *Lasers Surg Med* 2012;44:144–51.
238. Santiago FR, Piscoya M, Chi YW. Change in perception of sclerotherapy results after exposure to pre-post intervention photographs. *Phlebology*. 2018;33:282-87.
239. Meissner MH, Gloviczki P, Comerota AJ et al. Early thrombus removal strategies for acute deep venous thrombosis: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2012 ;55:1449-62.
240. NICE guidelines 2012. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. <https://www.nice.org.uk/guidance/cg144/chapter/Context>.
241. Nicolaides AN, Fareed J, Kakkar AK et al. Prevention and treatment of venous thromboembolism--International Consensus Statement. *Int Angiol*. 2013;32:111-260.
242. Vedantham S, Sista AK, Klein SJ et al. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol*. 2014;25:1317-325.
243. Kahn SR, Comerota AJ, Cushman M, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014;130(16):1636-661.

244. Management of Obstruction of the Femoroiliocaval Venous System. American Vein and Lymphatic Society. <http://www.phlebology.org/wp-content/uploads/2015/10/Management-of-Obstruction-of-the-Femoroiliocaval-Venous-System-Guidelines.pdf>
245. NICE guidelines 2015. Ultrasound-enhanced, catheter-directed thrombolysis for deep vein thrombosis. <https://www.nice.org.uk/guidance/ipg523>
246. Mazzolai L, Aboyans V, Ageno W, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European society of cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. *Eur Heart J*. 2018;39:4208-218.
247. NICE 2019 <https://www.nice.org.uk/guidance/indevelopment/gid-ipg10086>.
248. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. *Lancet Haematol*. 2016;3:e64-71.
249. Vedantham S, Piazza G, Sista AK, et al. Guidance for the use of thrombolytic therapy for the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41:68-80.
250. Vedantham S, Goldhaber SZ, Julian JA, et al. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. *N Engl J Med*. 2017;377:2240-52.
251. Marston WA. Results of the ATTRACT trial do not change the management of acute deep vein thrombosis. *J Vasc Surg Venous Lymphat Disord*. 2018;6:5-6.
252. Kearon C, Gu CS, Julian JA, et al. Pharmacomechanical Catheter-Directed Thrombolysis in Acute Femoral-Popliteal Deep Vein Thrombosis: Analysis from a Stratified Randomized Trial. *Thromb Haemost*. 2019;119:633-44.
253. Comerota AJ, Kearon C, Gu CS, et al. Endovascular Thrombus Removal for Acute Iliofemoral Deep Vein Thrombosis. *Circulation*. 2019;139:1162-73.

254. Tang T, Chen L, Chen J et al. Pharmacomechanical Thrombectomy Versus Catheter-Directed Thrombolysis for Iliofemoral Deep Vein Thrombosis: A Meta-Analysis of Clinical Trials. *Clin Appl Thromb Hemost*. 2019;25:1076029618821190.
255. Wong PC, Chan YC, Law Y, et al. Percutaneous mechanical thrombectomy in the treatment of acute iliofemoral deep vein thrombosis: a systematic review. *Hong Kong Med J*. 2019;25:48-57.
256. Seager MJ, Busuttil A, Dharmarajah B et al. Editor's Choice – A Systematic Review of Endovenous Stenting in Chronic Venous Disease Secondary to Iliac Vein Obstruction. *Eur J Vasc Endovasc Surg*. 2016;51:100-20.
257. Rizvi SA, Ascher E, Hingorani A, et al. Stent patency in patients with advanced chronic venous disease and non-thrombotic iliac vein lesions. *J Vasc Surg Venous Lymphat Disord*. 2018;6:457-63.
258. van Vuuren TMAJ, Doganci S, Wittens CHA. Patency rates and clinical outcomes in a cohort of 200 patients treated with a dedicated venous stent. *J Vasc Surg Venous Lymphat Disord*. 2018;6:321-329.
259. Zamboni P, Franceschi C, Del Frate R. The overtreatment of illusory May Thurner syndrome. *Veins & Lymphatics* 2019;8:8020.
260. Gagne PJ, Tahara RW, Fastabend CP et al. Venography versus intravascular ultrasound for diagnosing and treating iliofemoral vein obstruction. *J Vasc Surg Venous Lymphat Disord*. 2017;5:678-87.
261. Gagne PJ, Gasparis A, Black S, et al. Analysis of threshold stenosis by multiplanar venogram and intravascular ultrasound examination for predicting clinical improvement after iliofemoral vein stenting in the VIDIO trial. *J Vasc Surg Venous Lymphat Disord*. 2018;6:48-56.e1.
262. van Vuuren TM, van Laanen JHH, de Geus M, et al. A randomised controlled trial comparing venous stenting with conservative treatment in patients with deep venous obstruction: research protocol. *BMJ Open*. 2017;7:e017233.
263. van Vuuren TMAJ, Kurstjens RLM, Wittens CHA, et al. Illusory Angiographic Signs of Significant Iliac Vein Compression in Healthy Volunteers. *Eur J Vasc Endovasc Surg*. 2018;56:874-79.

264. Trinh F, Paolini D, Fish J, et al. Use of Villalta Score for Defining Post-Thrombotic Disease May Lead to False-Positive Diagnosis in 42% of Patients With Primary Chronic Venous Disease. *J Vasc Surg Venous Lymphat Disord*. 2018;2:291.
265. Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers. [https://www.nzwcs.org.nz/images/luag/2011\\_awma\\_vlug.pdf](https://www.nzwcs.org.nz/images/luag/2011_awma_vlug.pdf)
266. Neumann HAM, et al. Evidence-based (S3) guidelines for diagnostics and treatment of venous leg ulcers. *J Eur Acad Dermatol Venereol*. 2016;30:1843-875
267. Bush R, Comerota A, Meissner M, et al. Recommendations for the medical management of chronic venous disease: The role of Micronized Purified Flavanoid Fraction (MPFF). Recommendations from the Working Group in Chronic Venous Disease (CVD) 2016. *Phlebology* 2017;32:3–19.
268. Jiang QJ, Bai J, Jin J, et al. Sulodexide for Secondary Prevention of Recurrent Venous Thromboembolism: A Systematic Review and Meta-Analysis. *Front Pharmacol*. 2018;9:876.
269. Morling JR, Broderick C, Yeoh SE, et al. Rutosides for treatment of post-thrombotic syndrome. *Cochrane Database Syst Rev*. 2018;11:CD005625.
270. Carroll BJ, Piazza G, Goldhaber SZ. Sulodexide in venous disease. *J Thromb Haemost*. 2019;17:31-8.
271. Kakkos SK, Nicolaides AN. Efficacy of micronized purified flavonoid fraction (Daflon®) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. *Int Angiol*. 2018;37:143-54.
272. Ulloa JH. Micronized Purified Flavonoid Fraction (MPFF) for Patients Suffering from Chronic Venous Disease: A Review of New Evidence. *Adv Ther*. 2019; 36(Suppl 1):20-25.
273. Varatharajan L, Thapar A, Lane T et al. Pharmacological adjuncts for chronic venous ulcer healing: a systematic review. *Phlebology*. 2016;3:356-65.
274. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM, et al. Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev*. 2016;4:CD003229.

275. González Ochoa A. Sulodexide and phlebotonics in the treatment of venous ulcer. *Int Angiol.* 2017;36:82-7.
276. Lumley E, Phillips P, Aber A et al. Experiences of living with varicose veins: A systematic review of qualitative research. *J Clin Nurs.* 2019;28:1085-99.
277. Phillips P, Lumley E, Duncan R et al. A systematic review of qualitative research into people's experiences of living with venous leg ulcers. *J Adv Nurs.* 2018;74:550-63.
278. Norman G, Westby MJ, Rithalia AD et al. Dressings and topical agents for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2018;6:CD012583.
279. Gohel MS, Heatley F, Liu X et al. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. *N Engl J Med.* 2018;378:2105-114.
280. Davies HO, Popplewell M, Bate G, et al. Publication of UK NICE Clinical Guidelines 168 has not significantly changed the management of leg ulcers in primary care: An analysis of The Health Improvement Network database. *Phlebology.* 2018 Oct 18;268355518805658. doi: 10.1177/0268355518805658. [Epub ahead of print]
281. Dumville JC, Land L, Evans D et al. Negative pressure wound therapy for treating leg ulcers. *Cochrane Database Syst Rev.* 2015:CD011354.
282. Leclercq A, Labeille B, Perrot JL, et al. Skin graft secured by VAC (vacuum-assisted closure) therapy in chronic leg ulcers: A controlled randomized study. *Ann Dermatol Venereol.* 2016;143:3-8.
283. Serra R, Rizzuto A, Rossi A et al. Skin grafting for the treatment of chronic leg ulcers - a systematic review in evidence-based medicine. *Int Wound J.* 2017;14:149-57.
284. Zollino I, Zuolo M, Giancesini S, et al. Autologous adipose-derived stem cells: Basic science, technique, and rationale for application in ulcer and wound healing. *Phlebology.* 2017;32:160-71.
285. Maccatrozzo S, Onida S and Davies AH. Guidelines on venous ulceration: A mess. *Phlebology* 2017;32:369–70.
286. Tan MKH, Luo R, Onida S, et al. Venous Leg Ulcer Clinical Practice Guidelines: What is AGREEd? *Eur J Vasc Endovasc Surg.* 2019;57:121-29.

287. Falanga V, Saap LJ, Ozonoff A. Wound bed score and its correlation with healing of chronic wounds. *Dermatol Ther.* 2006;19:383-90.
288. International Lymphoedema Framework. International consensus: best practice for the management of lymphoedema. London: MEP Ltd. 2006
289. Michelini S, Campisi C, Ricci M et al. Linee guida italiane sul linfedema. *Eur Med Phys.* 2007;43:1-4.
290. Lee BB, Andrade M, Antignani PL et al. Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2013. *Int Angiol.* 2013;32:541-74.
291. Stillo F, Baraldini V, Dalmonte P et al. Vascular Anomalies Guidelines by the Italian Society for the study of Vascular Anomalies (SISAV). *Int Angiol.* 2015;34:1-45.
292. Lee BB, Antignani PL, Baroncelli TA et al. IUA-ISVI consensus for diagnosis guideline of chronic lymphedema of the limbs. *Int Angiol.* 2015;34:311-32.
293. Executive Committee. The Diagnosis and Treatment of Peripheral Lymphedema: 2016 Consensus Document of the International Society of Lymphology. *Lymphology.* 2016;49:170-184.
294. Ciucci JL. VI Latin American consensus for the treatment of lymphedema. 2017. <http://www.centrociucci.com.ar/descargas/6-Consenso-2017-nuevo3.pdf>
295. Halk A-B, Damstra RJ, Halk B et al. The Dutch lymphedema guidelines based on the International Classification of Functioning, Disability, and Health and the chronic care model. *Journal of Vascular Surgery: Venous and Lymphatic Disorders.* *J Vasc Surg Venous Lymphatic Disord.* 2017;5:756-65.
296. Maclellan RA, Greene AK. Lymphoedema. *BMJ Best Practice.* 2018. [BMJ.https://bestpractice.bmj.com/topics/en-gb/610](https://bestpractice.bmj.com/topics/en-gb/610)
297. Slavin SA, Greene AK, Borud LJ. Lymphedema. In: Weinzwieg J, ed. *Plastic surgery secrets plus.* 2nd ed. Philadelphia, PA: Mosby; 2009.
298. The Diagnosis And Treatment Of Lymphedema: Position Statement of the National Lymphedema Network. <https://www.mylymph.com/2018/03/08/the-diagnosis-and-treatment-of-lymphedema-position-statement-of-the-national-lymphedema-network>.
299. Cormier JN, Rourke L, Crosby M, et al. The surgical treatment of lymphedema: a systematic review



- of the contemporary literature (2004-2010). *Ann Surg Oncol*. 2012;19:642-51.
300. Hadamitzky C, Pabst R, Gordon K, et al. Surgical procedures in lymphedema management. *J Vasc Surg Venous Lymphat Disord*. 2014;2:461-8.
301. Carl HM, Walia G, Bello R et al. Systematic Review of the Surgical Treatment of Extremity Lymphedema. *J Reconstr Microsurg*. 2017;33:412-25.
302. Campisi CC, Ryan M, Villa G, et al. Rationale for Study of the Deep Subfascial Lymphatic Vessels During Lymphoscintigraphy for the Diagnosis of Peripheral Lymphedema. *Clin Nucl Med*. 2019;44:91-8.
303. Partsch H. Compression Therapy: Clinical and Experimental Evidence. *Ann Vasc Dis*. 2012;5:416–22.
304. Schaverien M, Moeller J, Cleveland S. Nonoperative Treatment of Lymphedema. *Semin Plast Surg*. 2018;32:17-21.
305. Lee BB. State of art in lymphedema management: part 1. *Phlebology* - Vol 25. No. 2. 2018;25:160-71.
306. Lee BB. State of art in lymphedema management: part 2. *Phlebology* - Vol 25. No. 3. 2018;25:189-200
307. Chengelis DL, Bendick PJ, Glover JL, et al. Progression of superficial venous thrombosis to deep vein thrombosis. *J Vasc Surg*. 1996;24:745-9.
308. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e419S-e96S.
309. Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363:1222-32.
310. Righini M, Paris S, Le Gal G, et al. Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost*. 2006;95:56-64.
311. Galanaud JP, Sevestre-Pietri MA, et al. Comparative study on risk factors and early outcome of

- symptomatic distal versus proximal deep vein thrombosis: results from the OPTIMEV study. *Thromb Haemost.* 2009;102:493-500.
312. Lagerstedt CI, Olsson CG, Fagher BO, et al. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. *Lancet.* 1985;2:515-18.
313. Palareti G, Cosmi B, Lessiani G, et al. Evolution of untreated calf deep-vein thrombosis in high risk symptomatic outpatients: the blind, prospective CALTHRO study. *Thromb Haemost.* 2010;104:1063-70.
314. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. *Circulation.* 2003;107(23 Suppl 1):I17-21.
315. Akl EA, Kahale L, Barba M, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev.* 2014:CD006650.
316. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med.* 2006;355:1780-9.
317. Wong A, Kraus PS, Lau BD, et al. Patient preferences regarding pharmacologic venous thromboembolism prophylaxis. *J Hosp Med.* 2015;10:108-11.
318. Blondon M, Righini M, Bounameaux H, et. Fondaparinux for isolated superficial vein thrombosis of the legs: a cost-effectiveness analysis. *Chest.* 2012;141:321-9.
319. Decousus H, Quere I, Presles E, et al. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. *Ann Intern Med.* 2010;152:218-24.
320. Beyer-Westendorf J, Schellong SM, Gerlach H, et al. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. *Lancet Haematol.* 2017;4:e105-e13.
321. Righini M. Is it worth diagnosing and treating distal deep vein thrombosis? No. *J Thromb Haemost.* 2007;5 Suppl 1:55-9.
322. Righini M, Galanaud JP, Guennevez H, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. *Lancet Haematol.*

2016;3:e556-e62.

323. Parisi R, Visona A, Camporese G, et al. Isolated distal deep vein thrombosis: efficacy and safety of a protocol of treatment. Treatment of Isolated Calf Thrombosis (TICT) Study. *Int Angiol.* 2009;28:68-72.
324. Vedovati MC, Germini F, Agnelli G, et al. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest.* 2015;147:475-83.
325. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med.* 2018;378:615-24.
326. Young AM, Marshall A, Thirlwall J, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). *J Clin Oncol.* 2018;36:2017-23.
327. Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2018;16:1891-4.
328. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;349:631-9.
329. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med.* 2017;376:1211-222.
330. Agnelli G, Buller HR, Cohen A, Curto M, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368:699-708.
331. Simes J, Becattini C, Agnelli G, et al. Aspirin for the prevention of recurrent venous thromboembolism: the INSPIRE collaboration. *Circulation.* 2014;130:1062-71.
332. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med.* 2012;366:1959-67.
333. Cohen AT, Hamilton M, Bird A, et al. Comparison of the Non-VKA Oral Anticoagulants Apixaban, Dabigatran, and Rivaroxaban in the Extended Treatment and Prevention of Venous Thromboembolism:

- Systematic Review and Network Meta-Analysis. PLoS One. 2016;11:e0160064.
334. Rollins BM, Silva MA, Donovan JL, et al. Evaluation of oral anticoagulants for the extended treatment of venous thromboembolism using a mixed-treatment comparison, meta-analytic approach. Clin Ther. 2014;36:1454-464.
335. McKinlay J, Link C, Marceau L, et al. How do doctors in different countries manage the same patient? Results of a factorial experiment. Health Serv Res. 2006;41:2182-200. Erratum in: Health Serv Res. 2006;41:2303.
336. Takayama A, Narukawa M. Pharmaceutical Pricing and Reimbursement in Japan: For Faster, More Complete Access to New Drugs. Ther Innov Regul Sci. 2016;50:361-367.
337. Rump A, Schöffski O. [The Japanese Health Care System: An Analysis of the Funding and Reimbursement System]. Gesundheitswesen. 2018 ;80:897-909.
338. Kane RL. Creating practice guidelines: the dangers of over-reliance on expert judgment. J Law Med Ethics. 1995;23:62-4.
339. Pae CU. Why Systematic Review rather than Narrative Review? Psychiatry Investig. 2015 Jul;12(3):417-9.