

## REVIEW



# Fake-news-free evidence-based communication for proper vein-lymphatic disease management

Sergio GIANESINI <sup>1</sup> \*, Yung-Wei CHI <sup>2</sup>, Chantal AGÜERO <sup>3</sup>, Deena ALQEDRAH <sup>4</sup>, Miguel AMORE <sup>5</sup>, Mohammad BARBATI <sup>6</sup>, Adriana BATURONE <sup>7</sup>, Stephen BLACK <sup>8</sup>, Denis BORSUK <sup>9</sup>, Oscar BOTTINI <sup>10</sup>, Joseph CAPRINI <sup>11</sup>, Marilyn CHAMO <sup>12</sup>, Meena CHERIAN <sup>13</sup>, Larisa CHERNUKA <sup>14</sup>, Marianne DE MAESENEER <sup>15</sup>, José DIAZ <sup>16</sup>, Mark J. GARCIA <sup>17</sup>, Kathleen GIBSON <sup>18</sup>, Monika GLOVICZKI <sup>19</sup>, Peter GLOVICZKI <sup>20</sup>, Veronika GOLOVINA <sup>21</sup>, Elena GORANOVA <sup>22</sup>, Lorena GRILLO <sup>23</sup>, Adam GWOZDZ <sup>24</sup>, Tobias HIRSCH <sup>25</sup>, Emad HUSSEIN <sup>26</sup>, Ernesto INTRIAGO <sup>27</sup>, Houman JALAIE <sup>6</sup>, Aleksandra JAWORUCKA-KACZOROWSKA <sup>28</sup>, Ravul JINDAL <sup>29</sup>, Matthieu JOSNIN <sup>30</sup>, Neil M. KHILNANI <sup>31</sup>, Dong-Ik KIM <sup>32</sup>, Alejandro LATORRE <sup>33</sup>, Zaza LAZARASHVILI <sup>34</sup>, Byung-Boong LEE <sup>35</sup>, Luis LEON <sup>36</sup>, Ngho C. LIEW <sup>37</sup>, Kirill LOBASTOV <sup>21</sup>, Fedor LURIE <sup>38</sup>, Annalisa MAGHETTI <sup>39</sup>, Erica MENEGATTI <sup>1</sup>, Kasuo MIYAKE <sup>40</sup>, Makoto MO <sup>41</sup>, Sriram NARAYANAN <sup>42</sup>, Diana NEUHARDT <sup>43</sup>, Felizitas PANNIER <sup>44</sup>, Alfredo PREGO <sup>45</sup>, Eberhard RABE <sup>44</sup>, Joseph RAFFETTO <sup>46</sup>, Pauline RAYMOND-MARTIMBEAU <sup>47</sup>, Laura REDMAN <sup>48</sup>, Lourdes REINA-GUTIERREZ <sup>49</sup>, Rodrigo RIAL <sup>50</sup>, Stanley ROCKSON <sup>51</sup>, Marco ROMANELLI <sup>52</sup>, Fabricio R. SANTIAGO <sup>53</sup>, Raquel A. SANTIAGO <sup>53</sup>, Nuttawut SERMSATHANASAWADI <sup>54</sup>, Evgeny SHAYDAKOV <sup>55</sup>, Carlos SIMKIN <sup>56</sup>, Joel SOUSA <sup>57</sup>, Julianne STOUGHTON <sup>46</sup>, Andrzej SZUBA <sup>58</sup>, Wassila TAHA <sup>59</sup>, Jorge ULLOA <sup>60</sup>, Tomasz URBANEK <sup>61</sup>, Marco VITALE <sup>62</sup>, Marc VUYLSTEKE <sup>63</sup>, Jinsong WANG <sup>64</sup>, Janaina WEINGARTNER <sup>65</sup>, Spencer WILSON <sup>66</sup>, Takashi YAMAKI <sup>67</sup>, Yeejia NG <sup>42</sup>, Igor ZOLOTUKHIN <sup>21</sup>, Armando MANSILHA <sup>57</sup>

**Congresses.**—Scientific results of the official project presented during the Universal EXPO (World Fair) DUBAI on Feb 5 2022, endorsed by 71 vascular scientific societies, recognized by the Communication Coordination Committee for the United Nations.

<sup>1</sup>Department of Translational Medicine, University of Ferrara, Ferrara, Italy; <sup>2</sup>University of California Davis, Sacramento, CA, USA; <sup>3</sup>Panamerican Society of Phlebology and Lymphology, Asunción, Paraguay; <sup>4</sup>Dubai Health Authority-University of Sharjah, Dubai, United Arab Emirates; <sup>5</sup>University of Buenos Aires, Buenos Aires, Argentina; <sup>6</sup>RWTH University Hospital of Aachen, Aachen, Germany; <sup>7</sup>University Hospital of Guadalajara, Guadalajara, Spain; <sup>8</sup>Guy's & St Thomas' NHS Foundation Trust, London, UK; <sup>9</sup>Clinic of Phlebology and Laser Surgery (Vasculab LLC), Chelyabinsk, Russia; <sup>10</sup>German Hospital, Buenos Aires, Argentina; <sup>11</sup>NorthShore University, Chicago, IL, USA; <sup>12</sup>Guatemala Society of Phlebology, Guatemala City, Guatemala; <sup>13</sup>Geneva Foundation for Medical Education and Research, Geneva, Switzerland; <sup>14</sup>O.O. Shalimov National Institute of Surgery and Transplantology, Kiev, Ukraine; <sup>15</sup>Erasmus Medical Center, Rotterdam, the Netherlands; <sup>16</sup>Vanderbilt University, Nashville, TN, USA; <sup>17</sup>Endovascular Consultants, Wilmington, NC, USA; <sup>18</sup>Lake Washington Vascular Surgeons, Seattle, WA, USA; <sup>19</sup>Vascular Science & Art, Scottsdale, AZ, USA; <sup>20</sup>Mayo Clinic, Rochester, MN, USA; <sup>21</sup>Pirogov Russian National Research Medical University, Moscow, Russia; <sup>22</sup>Alexandrovskaya University Medical Center, Sofia, Bulgaria; <sup>23</sup>UCIMED University of Medical Sciences, San José, Costa Rica; <sup>24</sup>Imperial College of London, London, UK; <sup>25</sup>Vein Competency Center, Halle, Germany; <sup>26</sup>Ain Shams University, Cairo, Egypt; <sup>27</sup>University Espíritu Santo, Guayaquil, Ecuador; <sup>28</sup>Jaworuccy Medical Center, Gorzów Wlkp, Poland; <sup>29</sup>Punjab University, Chandigarh, India; <sup>30</sup>French Society of Phlebology, Paris, France; <sup>31</sup>Weill Cornell Medicine, New York Presbyterian Hospital, New York, NY, USA; <sup>32</sup>Sungkyunkwan University, Seoul, South Korea; <sup>33</sup>Bucaramanga University, Bucaramanga, Colombia; <sup>34</sup>Chapdize Cardiovascular Center, Tbilisi, Georgia; <sup>35</sup>George Washington University, Washington, USA; <sup>36</sup>University of Arizona, Phoenix, AZ, USA; <sup>37</sup>University Putra Malaysia, Selangor, Malaysia; <sup>38</sup>Jobst Vascular Institute, Toledo, OH, USA; <sup>39</sup>Italian Association of Dietology and Clinical Nutrition, Bologna, Italy; <sup>40</sup>Hiroshi Miyake Study Center, São Paulo, Brazil; <sup>41</sup>Yokohama City University, Yokohama, Japan; <sup>42</sup>The Harley Street Heart and Vascular Center,

Singapore, Singapore; <sup>43</sup>Comprehensive Integrated Care Center, Phoenix, AZ, USA; <sup>44</sup>Private Practitioner, Bonn, Germany; <sup>45</sup>University of Montevideo, Montevideo, Uruguay; <sup>46</sup>Harvard University, Boston, MA, USA; <sup>47</sup>Canadian Society of Phlebology, Montreal, Canada; <sup>48</sup>Christiaan Barnard Memorial Hospital, Cape Town, South Africa; <sup>49</sup>Red Cross Hospital, Madrid, Spain; <sup>50</sup>University Hospital HM Madrid-Torrelodones, Madrid, Spain; <sup>51</sup>Stanford University, Stanford, CA, USA; <sup>52</sup>University of Pisa, Pisa, Italy; <sup>53</sup>Federal University of Goias, Goias, Brazil; <sup>54</sup>Mahidol University, Bangkok, Thailand; <sup>55</sup>Peter State University, St Petesbourg, Russia; <sup>56</sup>Latin America Venous Forum, Buenos Aires, Argentina; <sup>57</sup>University of Porto, Porto, Portugal; <sup>58</sup>Medical University of Wroclaw, Wroclaw, Poland; <sup>59</sup>Egypt Africa Venous Lymphatic Association, Cairo, Egypt; <sup>60</sup>Los Andes University, Bogotá, Colombia; <sup>61</sup>Medical University of Silesia, Katowice, Poland; <sup>62</sup>University of Parma, Parma, Italy; <sup>63</sup>Sint-Andries Ziekenhuis Tielt, Tielt, Belgium; <sup>64</sup>Provincial People's Hospital of Guangdong, Guangdong, China; <sup>65</sup>Hospital Nossa Senhora das Graças, Curitiba, Brazil; <sup>66</sup>University of Boston, Boston, MA, USA; <sup>67</sup>Women's Medical University Adachi Medical Center of Tokyo, Tokyo, Japan

\*Corresponding author: Sergio Giancesini, University of Ferrara, via Porta a Mare 11, 45100 Rovigo, Italy. E-mail: gnsrg@unife.it

## ABSTRACT

Published scientific evidence demonstrate the current spread of healthcare misinformation in the most popular social networks and unofficial communication channels. Up to 40% of the medical websites were identified reporting inappropriate information, moreover being shared more than 450,000 times in a 5-year-time frame. The phenomenon is particularly spread in infective diseases medicine, oncology and cardiovascular medicine. The present document is the result of a scientific and educational endeavor by a worldwide group of top experts who selected and analyzed the major issues and related evidence-based facts on vein and lymphatic management. A section of this work is entirely dedicated to the patients and therefore written in layman terms, with the aim of improving public vein-lymphatic awareness. The part dedicated to the medical professionals includes a revision of the current literature, summing up the statements that are fully evidence-based in venous and lymphatic disease management, and suggesting future lines of research to fulfill the still unmet needs. The document has been written following an intense digital interaction among dedicated working groups, leading to an institutional project presentation during the Universal Expo in Dubai, in the occasion of the v-WINter 2022 meeting.

(Cite this article as: Giancesini S, Chi YW, Agüero C, Alqedrah D, Amore M, Barbati M, *et al.* Fake-news-free evidence-based communication for proper vein-lymphatic disease management. *Int Angiol* 2023;42:89-189. DOI: 10.23736/S0392-9590.23.05044-7)

**Key words:** Disinformation; Saphenous vein; Lymphedema.

## Project rationale and aim

Modern world communication is characterized by the ease of access to information made possible by the digitalization and in particular by the social networks use. More than 3.5 billion of people are present in such networks and a significant part of them is getting information mainly from these online tools rather than from the official sources (<https://www.statista.com/topics/1164/social-networks/>, <https://www.pewresearch.org/journalism/fact-sheet/social-media-and-news-fact-sheet/>).<sup>1</sup> More than 40% of medical websites have been spotted to promote potential fake-news, shared more than 450.000 times in a 5 year-time frame.<sup>2</sup> The World Economic Forum has considered misinformation as one of the most significant is-

ssues facing the world since 2013 (<http://reports.weforum.org/outlook-14/>): an issue that affects both the elderly<sup>3</sup> and the new generation, so much to leading to evidence-based data publications officially calling experts and scientific societies for counteraction.<sup>4</sup> The present document is the answer to such call from a worldwide group of experts in vein-lymphatic disease by means of a dedicated scientific and educational project developed on the occasion of the Universal Expo in Dubai, during the v-WINter 2022 meeting. Key Opinion Leaders from 83 countries and 71 vascular scientific societies and institutions were recruited.

Cardiovascular disease has been reported among the first three medical fields affected by fake news, together with infectious disease medicine and oncology.<sup>5</sup> The difficulty of COVID-19 pandemic has represented an oppor-

tunity to highlight the urgency of counteracting what is now defined as an “infodemic” of inappropriate healthcare information.<sup>6</sup> Phlebo-lymphology field is heavily “contaminated” by inappropriate medical indication and commercials promoting not evidence-based treatments, device, garments and substances use. Considering the same fields include extremely common diseases such as chronic venous disease and lymphedema, as well as potentially lethal conditions such as venous thrombo-embolism, proper education and information on such topics is of paramount importance.<sup>7</sup> Main aim of the herein delivered project is the report of what is supported by evidence *vs.* what is a potential false claim or a still empirical finding in need of further scientific confirmation in the venous-lymphatic practice. The document includes parts dedicated to health professionals, together with layman’s term contributions for public vein-lymphatic awareness increase.

## Methodology

Twelve working groups were created including top experts from all continents, with balanced geographical and gender equality representation. Each working group was assigned to a specific domain of vein and lymphatic medicine. Each working group also included a new generation representative who worked with the top experts in the literature search and in the document drafting.

The new generation representative, assisted by the top experts of her/his domain, presented the preliminary findings to a global audience of 7023 attendees, in hybrid format, during the v-WINter DUBAI 10<sup>th</sup> international interuniversity meeting in Phlebology, Lymphology & Aesthetics, on the institutional occasion of the Universal Expo (World Fair). The domains topics were identified prior to the congress, by Delphi methodology, involving the 71 scientific societies members who were asked what are considered to be the most important aspects to be discussed for proper evidence-based vein-lymphatic practice. Once the 70% agreement was reached, the topics were further investigated by means of the literature search performed by the related working groups. A dedicated online platform was created to allow both experts and public from all around the world to report vein-lymphatic topics potentially affected by significant misinformation circulation. 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.

PubMed, Embase, Cinhal and the Cochrane were used as scientific sources. In case of data coming from not indexed and/or from non-English journals, they were included only if considered of paramount value for the specific topic analysis. Priority was given to meta-analysis and systematic reviews of the 2012-2022 time-frame. Other study designs were included if considered of significant importance. The authors selected the most important references per topic. In case of disagreement a majority vote was taken by the same authors to choose the most relevant papers to be included in the document. References not ranking among the top ones are reported however in dedicated lists so to guide interested readers into a deeper reading. Authors also pointed out eventually perceived biases found in the analyzed literature, together with needed future research lines. A section dedicated to public vein-lymphatic awareness was included in all the domains, summing up in a layman’s term the main message of all the topics of every domain. Another section highlights possible valuable future research lines on topics still in need of proper evidence-based support. References considered worthy to be read, but not of primary value, were included in lists made available online in the open access webpage dedicated to the project. A meta-analysis of all the data related to the many topics assessed by this literature revision is out of the project scope, therefore its content is to be considered as a bird-eye view provided by a large panel of top experts coming from all continents, with geographical and gender equality. It is the hope of the authors this massive global work can serve as a basis for specifically addressed research lines focusing on unmet needs eventually highlighted by the present literature search. 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 professionals or providers.

## Content

The document domains are reported herein, together with the involved international key opinion leaders and the new generation representatives, specifying the continent of origin, in respect of geographical global representation. Every domain includes up to 11 topics related to that specific phlebo-lymphology area. At the end of every domain, the leaflet reporting the public vein-lymphatic awareness evidence-based statements is reported.

The scientific content developed by the authors and the related educational messages developed also thanks to the help of non-health professionals representatives for layman's term use effectiveness verification are reported in the domains of this document. A digital sum up has also been made available online in a dedicated open access platform (<https://vwinfoundation.com/fake-news-free-project/>) were health professionals and public can still submit eventually encountered potential vein-lymphatic misinformation, in order to submit it to the inter-continental key opinion leaders involved in this project. To the best of our knowledge, this document represents the only available attempt to combine evidence-based data literature analysis and public health awareness promotion on vein-lymphatic topics. The results of this international teamwork, also involving institutions, could pave the way for a synergistic multi-specialty and inter-society reach out for appropriate vein-lymphatic global care.

## 1. Vein-lymphatic disease burden

### 1. Lower limb chronic venous disease and lymphatic disease burden

#### *Query used for the literature search*

((varicose vein[MeSH Terms]) OR (lymphedema[MeSH Terms])) AND (prevalence[MeSH Terms])

#### *Main findings*

Lower limb CVD prevalence worldwide is high and variably reported, ranging from 1% to 73% of women and from 2% to 56% of men.<sup>8</sup> Racial factors influence the disease manifestation. African-American race affected by CVD demonstrated more advanced stages at a younger age compared with the Caucasian counterpart.<sup>9</sup> The prevalence of CEAP class C2 disease has been reported highest in Western Europe and lowest in the Middle East and Africa. CVD prevalence has been found higher in female gender, but contradictory outcomes have been published based also on the assessed disease stage, with male gender potentially presenting even higher prevalence of milder CVD.<sup>8, 10</sup> Significant methodology differences across the epidemiology studies lead to the need of further proper investigations to assess the real burden of the disease around the globe. Further research studies should also address the coexistence of vein and lymphatic drainage impairment. Health and non-health professionals must be aware that a lymphedema condition can, independently or not, coexist with a vein drainage

issue. Indeed, lymphedema remains a hidden epidemic and scientific as well as public health attention should be addressed to both the primary and secondary causes of it, including cancer, trauma and iatrogenic related etiology. Prevalence data show how almost 40% of the affected population might be undertreated: the increase in the related awareness and proper management is of paramount importance considering also the possible morbidity and mortality associated with lymphatic complications, such as cellulitis.<sup>11</sup>

#### *Analyzed literature possible biases*

- Methodology and study population life-style heterogeneity in vein-lymphatic epidemiology assessment.
- Lack of epidemiology studies in lower limb primary and secondary lymphedema, in particular with proper assessment of the possibly concomitant vein component.

#### *Suggested next research lines*

- Multiracial vein and/or lymphatic disease burden assessment.
- Coexisting vein-lymphatic lower limb drainage impairment burden.

#### *Related statement in layman's term for public vein-lymphatic awareness*

More than 50% of the adults can present leg vein and/or lymphatic issues.

#### *Suggested pertinent extra readings*

- a) Rockson SG. Advances in Lymphedema. *Circ Res* 2021;128:2003-16.
- b) Nicolaides AN, Labropoulos N. Burden and Suffering in Chronic Venous Disease. *Adv Ther* 2019;36(Suppl 1):1-4.
- c) Davies A. The Seriousness of Chronic Venous Disease: A Review of Real-World Evidence. *Adv Ther* 2019;36:S5-12.
- d) Dua A, Desai SS, Heller JA. The Impact of Race on Advanced Chronic Venous Insufficiency. *Ann Vasc Surg* 2016;34:152-6.
- e) Robertson L, Lee AJ, Evans CJ, Boghossian S, Allan PL, Ruckley CV, *et al*. Incidence of chronic venous disease in the Edinburgh Vein Study. *J Vasc Surg Venous Lymphat Disord* 2013;1:59-67.

## 2. Venous and lymphatic swelling

#### *Query used for the literature search*

swelling AND (lower limb)

### Main findings

The interconnection between venous and lymphatic systems has been clearly described decades ago.<sup>12</sup> Nevertheless, the mutual interdependence between veins and lymphatics function keeps on being not properly considered by the medical community. Vein drainage depends on lymphatic one and vice-versa. While one can compensate the other, in case of malfunctioning both of them can overload each other, as in the conditions of chronic venous hypertension and lymphedema. The two systems are inseparable and conjunctly involved in edema and swelling development: indeed, Starling principle has been revised taking into consideration the active lymphatic role in the capillary filtration process.<sup>13</sup> Lower limb swelling is an extremely common condition characterized by interstitial fluids accumulation, affecting both healthy subjects and vein-lymphatic patients. A proper knowledge of its pathophysiology is pivotal for proper care. Whenever dealing with a venous edema, the eventual lymphatic component should be assessed as well, and vice-versa. The approach must include a detailed history and sonographic assessment, including hemodynamic evaluation, in the field of venous and lymphatic insufficiency. Characterizing the fluidity of the edema is important as well in its potential to suggest an early vs. late stage of lymphatic involvement, even if not being sufficient to come to a final diagnosis. Lipedema must be taken into consideration in the swelling differential diagnosis, in order to prescribe an adequate treatment strategy.<sup>14</sup> Special attention should be paid in the detection of eventual drugs use leading to iatrogenic edema and worsening of the vein and/or lymphatic drainage. Lower limb swelling diagnostic work-up must always take into consideration systemic conditions leading to a lymphatic overload that might influence also the venous functionality, and viceversa.<sup>15</sup>

### Analyzed literature possible biases

Lack of objective measures and tools to clearly differentiate between lymphatic and vein functionality impairment.

### Suggested next research lines

Investigations assessing the grade of venous and lymphatic impairment reciprocal correlation.

### Related statement in layman's term for public vein-lymphatic awareness

In swollen legs both vein and lymphatic drainage must be properly assessed.

### Suggested pertinent extra readings

a) Raffetto JD, Khalil RA. Mechanisms of Lower Extremity Vein Dysfunction in Chronic Venous Disease and Implications in Management of Varicose Veins. *Vessel Plus* 2021;5:36.

b) Ortega MA, Fraile-Martínez O, García-Montero C, Álvarez-Mon MA, Chaowen C, Ruiz-Grande F, *et al.* Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. *J Clin Med* 2021;10:3239.

c) Rasmussen JC, Aldrich MB, Tan IC, Darne C, Zhu B, O'Donnell TF Jr, *et al.* Lymphatic transport in patients with chronic venous insufficiency and venous leg ulcers following sequential pneumatic compression. *J Vasc Surg Venous Lymphat Disord* 2016;4:9-17.

### 3. Venous and lymphatic disease coexistence prevalence

#### Query used for the literature search

((lymphedema) AND (venous)) AND (prevalence)

#### Main findings

Lower limb venous function impairment has been identified among the most common causes of lymphedema. Dean *et al.* reported more than 40% of lymphedema cases associated to venous hypertension.<sup>16</sup> Indeed, phlebo-lymphedema has been considered the most frequent cause of lymphedema in the western world. The progressively elongated life span of the population leads to an increase in the prevalence of cardiac pump failure, as well as in the use of medications that might aggravate the same lymphatic drainage. Obesity is a risk factor for both vein and lymphatic drainage impairment and it can represent *per se* a cause of venous and lymphatic failure, even in absence of vessel compromise. Moreover, obesity represents a potential obstruction to the drainage, therefore its management is of paramount importance in both chronic venous disease and lymphedema cases.<sup>17</sup> Preliminary data show how venous surgery can jeopardize the lymphatic integrity and evidence is missing on which therapeutic approach is best in terms of lymphatic function preservation. A condition of edema could then persist after the restoration of the normal vein flow, paradoxically following the same vein intervention.<sup>18</sup> On the contrary, data showed the possibility of a restoration of the lymphatic function following the vein drainage restoration, therefore demonstrating the need of a better understanding of the relationship between these two connected vascular systems.<sup>19</sup> All the above considerations, together with the lack of usually reported objective

vein and lymphatic functionality outcomes, make the real prevalence of vein and lymphatic dysfunction coexistence not possible to be currently assessed, but at the same time fundamental to be taken into consideration.

*Analyzed literature possible biases*

Lack of objective outcome measures differentiating vein and lymphatic disorders.

*Suggested next research lines*

Real world data on phlebo-lymphedema prevalence and incidence.

*Related statement in layman's term for public vein-lymphatic awareness*

Venous issues are among the main causes of lymphatic impairment.

*Suggested pertinent extra readings*

a) Dessalvi S, Villa G, Campisi CC, Boccardo F. Decreasing and preventing lymphatic-injury-related complications in patients undergoing venous surgery: A new diagnostic and therapeutic protocol. *Lymphology* 2018;51:57-65.

**4. C1 prevalence and clinical meaning**

*Query used for the literature search*

(chronic venous disease) AND (prevalence)

*Main findings*

Leg telangiectasias and reticular veins are a cosmetic complaint affecting more than 40% of the population, whose management is offered broadly around the world. Non-Hispanic whites and women have been reported to be more frequently affected. Telangiectasias, also known as spider veins, are defined as <1 mm dilated blood vessels on the surface of the skin. Reticular veins are <3 mm vessels located deeper in the skin. The related issue can be only cosmetic or also pathological, as potentially associated with symptoms such as pain, burning or itching. Possible risk factors for their appearance are family history, pregnancy, trauma, obesity and hormonal factors.<sup>20</sup> Considering more than 25% of the patients presenting telangiectasia are also affected by a deeper reflux leading to the venous hypertension, a proper history and diagnostic work-up is of paramount importance before whatever aesthetic management.<sup>21</sup> International guidelines are missing homogenous and solid indications identifying the best diagnostic and treatment protocol, an issue associated also with the lack

of comparative studies addressed to homogenous populations and related outcome measures.<sup>7</sup> It is important to point out that visible veins do not always indicate a severe functional disease and viceversa. Therefore, also apparently merely aesthetic vein concerns must be managed by experts in venous and lymphatic disease.<sup>22</sup>

*Analyzed literature possible biases*

Lack of homogeneous study population and standardized assessment.

*Suggested next research lines*

- Head to head comparison among the different techniques in homogenous study populations.
- Correlation between aesthetic vein issues and underlying hemodynamics.

*Related statement in layman's term for public vein-lymphatic awareness*

Aesthetic treatment of leg veins must always be preceded by a careful assessment also of the deeper veins by a specialist.

*Suggested pertinent extra readings*

a) Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. *J Epidemiol Community Health* 1999;53:149-53.

**5. C6 burden**

*Query used for the literature search*

(venous ulcer) AND burden

*Main findings*

Venous insufficiency is the most frequent cause of skin ulceration, accounting for approximately 70% of the cases. Its prevalence is over 1% of the population, reaching up to 2% in the over 80 yo patients. Recurrence risk remains high and above 60%.<sup>23</sup> These data show the significant burden venous ulceration represents, also for the health-economic cost associated with the disease. Recent data showed also the frequent association of venous leg ulcer with deep venous reflux, reporting the related extra-burden of the disease.<sup>24</sup> With the COVID-19 pandemic, further issues have been brought by the disease management in a lockdown and sedentary time, moreover characterized by the endothelial inflammation consequences associated with the same COVID infection. Proper patient educa-

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tion and self-management demonstrated their relevance in this challenging time. A recent cost-effectiveness analysis confirmed a cost over 1% of the annual national budget dedicated to this disease, with the biggest expense coming from the nursing visits: other data suggesting the importance of proper wound care and self-management development.<sup>25</sup> Preliminary data suggest that African-American patients tend to present with advanced disease stages and at a younger age, but further investigations are needed to determine the real burden of venous ulceration in different national and social contexts.<sup>9</sup>

#### Analyzed literature possible biases

Only not complicated ulcers have been usually included in the literature dedicated to wound care.

#### Suggested next research lines

Multinational registry creation for woundcare clinical and cost efficacy assessment.

#### Related statement in layman's term for public vein-lymphatic awareness

Venous ulceration affects more than 1% of the population and it must be promptly and properly assessed by a vascular expert.

#### Suggested pertinent extra readings

a) Ortega MA, Fraile-Martínez O, García-Montero C, Álvarez-Mon MA, Chaowen C, Ruiz-Grande F, *et al.* Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. *J Clin Med* 2021;10:3239.

b) Ren SY, Liu YS, Zhu GJ, Liu M, Shi SH, Ren XD, *et al.* Strategies and challenges in the treatment of chronic venous leg ulcers. *World J Clin Cases* 2020;8:5070-85.

### 6. Venous thromboembolism as leading cause of preventable death

#### Query used for the literature search

((varicose vein[MeSH Terms]) OR (lymphedema[MeSH Terms])) AND (prevalence[MeSH Terms])

#### Main findings

Currently, VTE incidence reported 115 cases per 100,000 and it is considered the third most frequent acute cardiovascular syndrome with rising incidence rates. While mortality may be decreased by the optimization of the diagnostic and therapeutic protocols, a possible incidence increase is to be expected following the elonga-

tion of the life span and the related negative influence of comorbidities representing a risk factor: obesity, cancer, heart failure, for example.<sup>26</sup> According to a recent review, cancer coexistence is associated with the highest VTE related death, therefore particular attention must be paid in this kind of patients management.<sup>27</sup> COVID pandemic brought an increased risk of thrombosis, for which prognostic factors have been identified in an age older than 60 years, in hypertension, in diabetes and in a D-Dimer values above 3.17 µg/mL.<sup>28</sup> The issue of VTE management in the elderly has been recently stressed by Yoo, pointing out the need of reducing the risk of bleeding by thrombolytic therapy, while counteracting a potentially lethal condition as the same VTE.<sup>29</sup> A call to action in increasing public health awareness on the VTE topic as leading cause of preventable death was done already back in 2015 by Lancet journal: such call remains extremely actual and needed.<sup>30</sup>

#### Analyzed literature possible biases

Different ultrasound venous scanning and thrombosis assessment protocols.

#### Suggested next research lines

- VTE detection in under-covered geographical areas.
- VTE risk proper stratification in different races.

#### Related statement in layman's term for public vein-lymphatic awareness

A clot in a leg vein (*thrombosis*) represents a leading cause of preventable death.

#### Suggested pertinent extra readings

a) Barco S, Mahmoudpour SH, Valerio L, Klok FA, Münzel T, Middeldorp S, *et al.* Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. *Lancet Resp Med* 2020;8:277-87.

b) Monreal M, Agnelli G, Chuang LH, Cohen AT, Gumbs PD, Bauersachs R, *et al.* Deep Vein Thrombosis in Europe-Health-Related Quality of Life and Mortality. *Clin Appl Thromb Hemost* 2019;25:1076029619883946.

c) Yoo HH. Thrombolysis in Pulmonary Embolism: Octagenarians Deserve More Attention! *Arq Bras Cardiol* 2022;118:75-6.

### 7. Age related thrombotic risk

#### Query used for the literature search

(age) AND (thrombosis)

*Main findings*

Venous thromboembolism prevalence has been reported to vary nearly 90 fold from <15 to >80 years old.<sup>31</sup> The phenomenon is in line with the pro-inflammatory and pro-thrombotic phenotype expression changes found in the red cells, platelets and on the endothelium of the aging population.<sup>32</sup> Indeed, VTE incidence is extremely rare in the young (<1 per 10,000 per year) but it increases up to ~1% per year in the over 60 yo. Between 25-30 years old, VTE is reported in about 1 per 10.000 patients, while at 85 years old it is found in 8 per 1000 subjects. The life-time risk of VTE at age 90 years old was demonstrated to be 15%. Therefore, aging is a major risk factor for VTE: a concept of particular importance considering the constantly increasing lifespan of the population. Immobilization has been identified among the main factors increasing the thrombotic risk in the elderly. Proper action should be taken to stimulate proper physical activity in the aging population.<sup>33</sup> COVID related thrombotic risk has also shown an age difference, with the over 65 yo presenting hypercoagulable states and excessive systemic inflammation compared to the younger population.<sup>34</sup>

*Analyzed literature possible biases*

Different comorbidities not excluded from the study populations, therefore potentially altering the assessed patients coagulability.

*Suggested next research lines*

Age related thrombotic risk calculation in homogenous study populations, excluding confounding factors such as comorbidities.

*Related statement in layman's term for public vein-lymphatic awareness*

Venous thrombosis risk increases rapidly with the age.

*Suggested pertinent extra readings*

a) Eichinger S, Kyrle PA. Sex, age and venous thrombosis-Are men and women indeed from different planets? Eur J Intern Med 2021;84:16-7.

b) Barco S, Klok FA, Mahé I, Marchena PJ, Ballaz A, Rubio CM, et al.; RIETE Investigators. Impact of sex, age, and risk factors for venous thromboembolism on the initial presentation of first isolated symptomatic acute deep vein thrombosis. Thromb Res 2019;173:166-71.

c) Cushman M. Epidemiology and risk factors for venous thrombosis. Semin Hematol 2007;44:62-9.

**8. Post-thrombotic syndrome burden**

*Query used for the literature search*

(post-thrombotic syndrome) AND ((burden) OR (prevalence) OR (incidence))

*Main findings*

Around 25% of patients affected by a first episode of deep venous thrombosis develop a post-thrombotic syndrome in the following 2 years.<sup>35</sup> The same post-thrombotic syndrome diagnosis is not univocal in the different centers around the world, therefore even the incidence and related burden has been reported in a heterogenous way in the scientific literature, reaching up to 60% of individuals previously affected by a deep venous thrombosis. Up to 10% of thrombotic patients are expected to develop skin ulceration in the following 2 years. The risk of symptoms and signs related to post-thrombotic syndrome has been reported along many years following the first thrombotic episode, highlighting the need of a constant patient care, together with proper public health awareness development. Risk factors for post-thrombotic syndrome development have been identified in proximal vs. distal thrombosis, obesity, persistent D-dimer elevation, contralateral limb deep venous thrombosis, recurrent thrombosis, severe valvular incompetence, advancing age and varicose veins. Nevertheless, making an objective assessment of post-thrombotic syndrome risk factors and burden is particularly challenging since there is no global standardization and agreement in the definition and in the severity scoring.<sup>36</sup> Post-thrombotic syndrome demonstrated to be an extremely expensive complication of deep venous thrombosis in several countries, contributing to more than 80% of the cost associated with the same thrombosis. Therefore, post-thrombotic syndrome prevention becomes mandatory for both patient proper management and for health-cost control.<sup>37</sup>

*Analyzed literature possible biases*

Lack of globally agreed post-thrombotic syndrome definition and scoring with consequent heterogeneity in burden assessment.

*Suggested next research lines*

Global consensus on post-thrombotic syndrome definition and scoring.

*Related statement in layman's term for public vein-lymphatic awareness*

More than 50% of patients experiencing a leg thrombosis (clot) might develop complications in the following years.

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### *Suggested pertinent extra readings*

a) Chopard R, Albertsen IE, Piazza G. Diagnosis and Treatment of Lower Extremity Venous Thromboembolism: A Review. JAMA 2020;324:1765-76.

## **9. Venous thrombosis recurrence**

### *Query used for the literature search*

((venous thrombosis) AND (recurrence)) AND ((incidence) OR (prevalence))

### *Main findings*

Venous thrombo-embolism recurrence has been reported to be over 30% after 10 years from the completion of the anticoagulation therapy. Up to 4% of these cases are fatal.<sup>38</sup> A distinction between provoked and unprovoked venous thrombo-embolism has been done also in terms of recurrence risk, with the first one occurring approximately in 3% of cases at 5 years versus up to 30% in the latter case. Several clinical prediction models are available for assessing the venous thrombo-embolism recurrence risk following an unprovoked event: for example, HERDOO2 score, Vienna prediction model, the DASH score, the Leiden Thrombosis Recurrence Risk Prediction model. While several biomarkers are currently investigated for venous thrombo-embolism recurrence prediction, up to our knowledge, none has been validated yet.<sup>39</sup> A recent publication showed how, in under 50 yo, family venous thrombo-embolism history represents a major risk for recurrence, independently by the gender.<sup>40</sup> Further risk factors for venous thrombo-embolism recurrence have been identified in antiphospholipid syndrome and active cancer. Venous thrombo-embolism associated with estrogen-containing contraceptives has a low risk of recurrence after hormonal therapy cessation.<sup>41</sup> The distinction between post-thrombotic syndrome and recurrent venous thrombo-embolism might be challenging due to overlapping sign and symptoms, together with a lack of diagnostic standards: further investigations on the specific characterization and identification of these two linked conditions are needed.

### *Analyzed literature possible biases*

Lack of proper distinction between post-thrombotic syndrome and venous thrombosis recurrence.

### *Suggested next research lines*

Validation of a globally accepted venous thrombosis clinical and instrumental follow-up protocol.

### *Related statement in layman's term for public vein-lymphatic awareness*

More than 1/4 thrombosis cases recur at 10 years from the first event.

### *Suggested pertinent extra readings*

a) Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost 2014;112:255-63.

## **10. Venous thrombosis genetic predisposition**

### *Query used for the literature search*

inherited thrombophilia

### *Main findings*

Last decades have been characterized by a significant increase in the knowledge of inherited thrombophilia. Inherited hypercoagulable states can be divided into 5 main categories:

1. qualitative or quantitative deficit of anti-coagulation (for example, antithrombin, protein C, protein S deficiency).
2. Increased activity of coagulation factors (for example, Activated protein C resistance and factor V Leiden, Prothrombin gene mutation (G20210A)).
3. Hyperhomocysteinemia.
4. Fibrinolytic system deficit.
5. Altered platelet function.<sup>42</sup>

In the general population, the prevalence of inherited hypercoagulation is reported to be 1 in 2500-5000 subjects and it increases to more than 10% in patients with a past history of thrombosis.<sup>43</sup>

Due the multitude of variables, the real prevalence is yet to be identified. A large registry evaluation reported at least 7% of the population presenting inherited thrombophilia. Interestingly, in this population no difference was reported between provoked and unprovoked thrombosis. The most frequently encountered thrombophilia in the registry was Factor V Leiden (26%) followed by antiphospholipid antibodies (20%) and prothrombin gene mutation (18%).<sup>44</sup> Sparse investigations dealt with the ethnical differences on inherited thrombophilia distribution. Further studies should be addressed to this topic. In general, testing should be considered in subjects belonging to families with a significant <50 years-old unprovoked VTE history. Testing should not be performed in case of clearly provoked events and in case of no changes in the anticoagulation strategies associated with the test result (Figure 1).<sup>45</sup>

in **Venous-lymphatic Veritas** consensus document

**Leg venous** and **lymphatic alterations** represent pathological conditions highly present in the population and often underdiagnosed and inadequately managed. **Fake information** is too easily found in the communication media. The present document includes up to **11 validated statements** per each and everyone of the **12 main domains** related to venous & lymphatic disease. This document is the result of an international consensus developed by **71 scientific societies and institutions**, by **more than 150 top experts**, from **83 countries**. Related **scientific references** and **educational content** are available in depth, in **multiple languages** and for both health professionals and population at the following website:

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**VEIN-LYMPHATIC DISEASE BURDEN**

1. More than 50% of the adults can present leg vein and/or lymphatic issues.
2. In swollen legs both vein and lymphatic drainage must be properly assessed.
3. Venous issues are among the main causes of lymphatic impairment.
4. Aesthetic treatment of leg veins must always be preceded by a careful assessment of the deeper veins by a specialist.
5. Venous ulceration affects more than 1% of the population and it must be promptly and properly assessed by a vascular expert.
6. A clot in a leg vein (*thrombosis*) represents a leading cause of preventable death.
7. Venous thrombosis risk increases rapidly with the age.
8. More than 50% of patients experiencing a leg thrombosis might develop complications in the following years.
9. More than ¼ thrombosis cases recur at 10 years from the first event.
10. Up to 7% of the population presents genetic predisposition to thrombosis.

**NO FAKE NEWS** in Veins & Lymphatic

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Figure 1.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding venous-lymphatic disease burden.

*Analyzed literature possible biases*

Possible selection bias in study populations including heterogeneous environmental risk factors.

*Suggested next research lines*

Multi-ethnicity inherited thrombophilia analysis.

*Related statement in layman’s term for public vein-lymphatic awareness*

Up to 7% of the population presents genetic predisposition to thrombosis.

*Suggested pertinent extra readings*

a) Ortega MA, Fraile-Martínez O, García-Montero C. Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. *J Clin Med* 2021;10:3239.

b) Connors JM. Thrombophilia Testing and Venous Thrombosis. *N Engl J Med* 2017;377:1177-87.

c) Baglin T, Gray E, Greaves M, Hunt BJ, Keeling D, Machin S, *et al.*; British Committee for Standards in Haematology. Clinical guidelines for testing for heritable thrombophilia. *Br J Haematol* 2010;149:209-20.

d) Buchanan GS, Rodgers GM, Branch DW. The inherited thrombophilias: genetics, epidemiology, and laboratory evaluation. *Best Pract Res Clin Obst Gynecol* 2003;138:128-34.

e) Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. *N Engl J Med* 2001;344:1222-31.

f) Maessen-Visch MB, Hamulyak K, Tazelaar DJ, Crombag NH, Neumann HA. The prevalence of factor V Leiden mutation in patients with leg ulcers and venous insufficiency. *Arch Dermatol* 1999;135:41-4.

**2. Venous diagnostics**

**1. Leg and pelvic venous scanning protocol**

*Query used for the literature search*

((“varicose veins”[MeSH Terms]) OR (“venous insufficiency”[MeSH Terms])) AND (“ultrasonography”[MeSH Terms])

*Main findings*

Venous ultrasound scanning is the pillar of phlebology diagnostic, yet it presents the challenge of being operator-dependent. In order to limit inter-observer variability and to maximize objective data production, validated scanning protocols for both lower limb and pelvic venous system must be followed. Similarities and controversies can be found in the papers and guidelines describing such protocols, for which global scientific synergy should be dedicated to the description of an internationally validated standardized lower limb and pelvic venous ultrasound assessment. This should include validated quantification of obstruction, specification of the effects of lying vs. semi-recumbent patient position during iliac stenosis hemodynamic assessment, follow-up timing and proper nomenclature use.<sup>7</sup> Venous reflux assessment should always be done in a standing or at least reverse Trendelenburg position in order to avoid underestimation of the same valvular incompetence. The assessed leg should be not-weight bearing in order to avoid muscle pump function activation and consequent systolic push on the venous system. Taking into consideration the time of the day and the season of the year is important for possible vessel caliber variation due to physical overload and temperature impact on the venous

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tone.<sup>46</sup> Hormonal variation might influence the venous hemodynamics as well.<sup>47</sup> In case of pelvic reflux suspect, a detailed scanning of the inferior vena cava, left renal vein, iliac veins, ovarian veins, trans and peri-uterine veins and the tributaries of the internal iliac veins should be performed.<sup>48</sup> IVUS demonstrated to be essential in iliac vein assessment for iliac vein stenting, therefore its use should always be considered in the suspect of a hemodynamically significant iliac stenosis potentially eligible to treatment.<sup>49</sup>

#### Analyzed literature possible biases

- Circadian, hormonal, seasonal hemodynamic variations influencing the scanning outcome.
- Lack of head-to-head comparison among different ultrasound scanning protocols.

#### Suggested next research lines

Validation of lower limb and pelvic international homogeneous scanning protocols.

#### Related statement in layman's term for public vein-lymphatic awareness

Echo-Doppler for lower limb venous disease detection must be performed with the patient in standing position. Pelvic sources of the disease must be excluded. IVUS (IVUS) should always be taken into consideration for possibly treatable conditions.

#### Suggested pertinent extra readings

a) Guideline developed in collaboration with the American College of Radiology; Society of Pediatric Radiology; Society of Radiologists in Ultrasound. AIUM practice guideline for the performance of peripheral venous ultrasound examinations. *J Ultrasound Med* 2015;34:1-95.

b) Khilnani NM. Duplex ultrasound evaluation of patients with chronic venous disease of the lower extremities. *AJR Am J Roentgenol* 2014;202:633-42.

c) Ganeshan A, Upponi S, Hon LQ, Uthappa MC, Warakaulle DR, Uberoi R. Chronic pelvic pain due to pelvic congestion syndrome: the role of diagnostic and interventional radiology. *Cardiovasc Intervent Radiol* 2007;30:1105-11.

d) Paschos GK, FitzGerald GA. Circadian clocks and vascular function. *Circ Res* 2010;106:833-41.

## 2. Venous reflux ultrasound appropriate detection

#### Query used for the literature search

((ultrasound) AND (venous)) AND (lower limb) AND (reflux)

#### Main findings

Lower limb venous ultrasound report quality and appropriateness varies significantly among the different national and international centers. Properly validated venous scanning protocols should be adopted worldwide for the sake of both patient valuable evaluation and scientific data comparison. Venous reflux threshold is set at 0.5 sec for the saphenous and its tributaries system, while it is at 1 sec for the femoral and popliteal axis. Reports should avoid only qualitative color imaging, rather favoring quantitative spectral analysis.<sup>50</sup> Perforating veins are considered incompetent whenever exhibiting an outward diastolic flow lasting more than 0.35 sec. Nevertheless, a careful assessment should include the perforator net flow direction considering data showing a low sensitivity of the outward diastolic flow only assessment.<sup>51</sup> More than one single maneuver should be adopted to elicit the flow considering a significantly different flow could be generated.<sup>52</sup> This is particularly evident at the sapheno-femoral junction, where the sample volume should be positioned at the femoral side of the terminal valve, evoking the flow by means of both Valsalva and compression/relaxation maneuvers in order to avoid false positive results.<sup>53</sup>

#### Analyzed literature possible biases

Not globally standardized assessment points and flow elicitation maneuvers for lower limb venous reflux detection.

#### Suggested next research lines

Validation of a standardized and reproducible global protocol for lower limb venous reflux assessment.

#### Related statement in layman's term for public vein-lymphatic awareness

Lower limb venous echo-Doppler report must include the deep, saphenous and superficial system findings.

#### Suggested pertinent extra readings

a) Chen CW, Tseng YH, Wong MY, Lin YH, Yang TY, Hsu YC, *et al.* Using Non-Contrast MRA to Discriminate between Obstructive and Nonobstructive Venous Diseases of the Legs. *Diagnostics (Basel)* 2021;11:1392.

b) Vitale C, D'Abate F, Froio A. Needs of standardisation in reporting a venous lower limb ultrasound exam for the assessment of varicose veins. *Phlebology* 2021;36:665-7.

c) Srisuwan T, Inmutto N, Kattipathanapong T, Rerkasem A, Rerkasem K, *et al.* Ultrasound Use in Diagnosis and Management of Venous Leg Ulcer. *Int J Low Extrem Wounds* 2020;19:305-14.

d) Marston WA, Brabham VW, Mendes R, Berndt D, Weiner M, Keagy B. The importance of deep venous reflux velocity as a determinant of outcome in patients with combined superficial and deep venous reflux treated with endovenous saphenous ablation. *J Vasc Surg* 2008;48:400-5; discussion 405-6.

### 3. Venous ultrasound reflux findings indicating treatment

#### Query used for the literature search

((venous ultrasound) AND (indication to treatment)) AND (lower limb)

#### Main findings

The absolute 0.5 and 1 sec reflux must always be integrated in the whole leg hemodynamics evaluation. The mere presentation of a flash reflux evoked in just a segment of the vessel is not sufficient to indicate pathology.<sup>50</sup> The presence of a saphenous laminar low velocity retrograde flow draining into a re-entry perforating vein is not *per se* a reflux indicating pathology and therefore treatment.<sup>54</sup> Indeed, the presence of a venous reflux did not show a change in venous disease progression in the Edinburgh Study.<sup>55</sup> The data show the importance of combining hemodynamic and clinical data before giving indication to treatment. Up to the knowledge of the authors, solid data on the indication to treatment are missing for the deep venous obstruction and/or reflux. The threshold of 50% stenosis has not yet been proved by significant evidence. A detailed IVUS assessment should be performed before eventual stenting in order also to minimize eventual complications related to the same procedure. The treatment should be proposed only in highly specialized centers after careful evaluation of the clinical impact of the hemodynamic disturbance.<sup>50</sup> In the context of pelvic venous disorders, the combination of hemodynamic and clinical parameters is of great importance as well. Pelvic vein dilation can not be considered *per se* indication to treatment as its incidental finding was detected in 47% of healthy subjects.<sup>56</sup>

#### Analyzed literature possible biases

- Lack of case-control comparison in venous stenting.
- Lack of hemodynamic biosignaling characterization.

#### Suggested next research lines

- Globally validated objective parameters to indicate treatment for deep venous obstruction and reflux.
- Mechanotransduction investigations.

#### Related statement in layman's term for public vein-lymphatic awareness

The identification of a venous reflux or dilation at the ultrasound is not enough for indicating a treatment.

#### Suggested pertinent extra readings

a) Schleimer K, Barbati ME, Grommes J, Hoeft K, Toonder IM, Wittens CHA, *et al.* Update on diagnosis and treatment strategies in patients with post-thrombotic syndrome due to chronic venous obstruction and role of endovenous recanalization. *J Vasc Surg Venous Lymphat Disord* 2019;7:592-600.

b) Teter KA, Maldonado TM, Adelman MA. A systematic review of venous aneurysms by anatomic location. *J Vasc Surg Venous Lymphat Disord* 2018;6:408-13.

c) Lopez AJ. Female Pelvic Vein Embolization: Indications, Techniques, and Outcomes. *Cardiovasc Intervent Radiol* 2015;38:806-20.

### 4. Venous ultrasound for superficial venous thrombosis

#### Query used for the literature search

((“venous thrombosis”[MeSH Terms]) AND (“lower extremity”[MeSH Terms])) AND (“ultrasonography”[MeSH Terms])

#### Main findings

Lower limb superficial venous thrombosis is a condition requiring awareness and management improvement. Few international guidelines are addressing the condition and no globally validated management protocol is currently available up to the knowledge of the authors. A concomitant contralateral superficial venous thrombosis has been reported in up to 25% of cases.<sup>7</sup> The deep venous thrombosis risk is increased in superficial venous thrombosis patients, particularly in case of cancer, previous superficial venous thrombosis not related to chronic venous disease, age>75yo, personal history of deep venous thrombosis. A concurrent deep venous thrombosis has been reported in up to 53% of SVT cases.<sup>57</sup> The data suggest the importance of a full leg bilateral ultrasound scanning, including both the superficial and deep venous system.<sup>58</sup> A recent publication pointed out the need of proper validated guidelines in superficial venous thrombosis ultrasound assessment, including the importance of routinely image the proximal 3 cm of the great saphenous vein, of assessing the eventual superficial venous thrombosis in districts of focal symptoms and of documenting the thrombus length and distance from confluences with the deep venous system.<sup>59</sup> Robust

data on the proper ultrasound follow-up timing are missing, therefore the authors suggest to adapt the protocol to the individual subject thrombotic risk, performing a scanning only in case its outcome is going to change the therapeutic plan.

*Analyzed literature possible biases*

Lack of homogenous international ultrasound protocols in superficial venous thrombosis detection.

*Suggested next research lines*

Comparison of different scanning protocols for superficial venous thrombosis detection.

*Related statement in layman's term for public vein-lymphatic awareness*

Superficial venous thrombosis identification at the ultrasound must always include both limbs and both the deep and superficial systems.

*Suggested pertinent extra readings*

- a) Roddy S. Superficial venous thrombosis and compression ultrasound imaging. *J Vasc Surg* 2012;56:1178.
- b) Décousus H, Bertolotti L, Frappé P, *et al.* Recent findings in the epidemiology, diagnosis and treatment of superficial-vein thrombosis. *Thromb Res* 2011;127 Suppl 3:S81-5.

**5. Venous ultrasound for deep venous thrombosis**

*Query used for the literature search*

((deep venous) AND (thrombosis)) AND (ultrasound) AND (protocol)

*Main findings*

Ultrasound scanning for deep venous thrombosis detection must always be integrated by a proper clinical risk score, for example Wells score, and lab evaluation. In case of unlikely clinical risk, a negative D-dimer can safely exclude deep venous thrombosis. Ultrasound scanning should be performed in case of likely clinical probability or in case of unlikely clinical probability but with a positive D-dimer and in all patients in which probability was not assessed. Up to the authors knowledge there is no globally validated ultrasound protocol for ultrasound deep venous thrombosis detection. Limiting the scanning above the knee might leave a significant risk of distal thrombosis and embolization, therefore a full leg scanning, including peroneal and posterior tibial veins, is suggested by the authors. Right and left common fem-

oral vein spectral analysis should be included to assess symmetry. Compression ultrasound maneuver should be performed every 2 cm in order to avoid false negative.<sup>60</sup> Special focus should be dedicated to symptomatic areas to exclude superficial venous thrombosis and/or other etiologies.<sup>61</sup> In case of distal deep venous thrombosis, serial imaging can be performed in carefully evaluated patients. A venous ultrasound scanning should be performed at 1 week or before if symptomatic, in order to assess possible extension.<sup>62</sup> Calf deep venous thrombosis scanning specificity has been reported to be over 97%, yet the sensitivity was found to be around 56%. Therefore, proper care in the follow-up of the serial scanning is fundamental.<sup>63</sup> In case of ilio-caval extension suspect, an ilio-caval ultrasound, computed tomography or magnetic resonance should be taken into consideration. Whatever diagnostic assessment should be scheduled if leading to a possible change in the patient management.

*Analyzed literature possible biases*

Surveillance timing heterogeneity in the different reports.

*Suggested next research lines*

Validation of a global protocol for deep venous thrombosis ultrasound scanning.

*Related statement in layman's term for public vein-lymphatic awareness*

Ultrasound scanning for deep venous thrombosis detection must include a specialist visit and it should cover all the leg with assessments every 2 cm.

*Suggested pertinent extra readings*

- a) Kearon C, de Wit K, Parpia S. Diagnosis of deep vein thrombosis with D-dimer adjusted to clinical probability: prospective diagnostic management study. *BMJ* 2022;376:e067378.
- b) Zhang S, Chu W, Wang H, Liang Y, Fan Y, Liu H, *et al.* Evaluation of stability of deep venous thrombosis of the lower extremities using Doppler ultrasound. *J Int Med Res* 2020;48:300060520942098.
- c) Naringrekar H, Sun J, Ko C, Rodgers SK. It's Not All Deep Vein Thrombosis: Sonography of the Painful Lower Extremity With Multimodality Correlation. *J Ultrasound Med* 2019;38:1075-89.
- d) *J Ultrasound Med* 2019;38:1075-89. Zuker-Herman R, Ayalon Dangur I, *et al.* Comparison between two-point and three-point compression ultrasound for the diagnosis of deep vein thrombosis. *J Thromb Thrombolysis* 2018;45:99-105.

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## 6. Venous flow phasicity in ultrasound thrombosis detection

### Query used for the literature search

((“venous”[Title/Abstract])) AND (“phasicity”[Title/Abstract])

### Main findings

A physiological phasicity exists among the ilio-femoral vein tract and the cardiac and respiratory motion. Venous thrombosis obstruction in between the cardio-respiratory pump and ilio-femoral tract can lead to a loss of this phasicity, which is considered a sign of possible thrombotic occlusion. In order to avoid false negative, it is mandatory to remind the presence of this phasicity can not exclude a thrombosis: for example, a collateral circulation could maintain the phasicity despite the thrombosis. An increase in the phasicity can be also the sign of a progressive recanalization of the previously obstructed vein tract and/or the consequence of a recently developed collateral circulation bypassing the thrombotic obstacle.<sup>64</sup> In this sense, the femoral way has been defined as a “window” to the pathology of the thorax, abdomen and pelvis. Waveform alterations at the femoral vein spectral analysis might indicate the need of cardiac, respiratory, abdominal and pelvic further investigations.<sup>65</sup> At the same time, the alteration of such waveform is not always pathological: respiratory phases can interact with the cardiac pattern and modify the femoral vein flow phasicity, even up to its disappearance.<sup>66</sup> In fact, direct observation of eventual correlations between atrial pressure and femoral vein flow characteristics demonstrated that the use of pulsatile Doppler ultrasonography in the common femoral vein is not reliable for diagnosing increases of the same atrium pressure. In conclusion, assessing carefully the femoral vein hemodynamics is of fundamental importance to suspect occlusion, obstructions, thorax and abdominal alterations, yet an integrated diagnostic approach is necessary before coming to the final diagnosis.<sup>67</sup>

### Analyzed literature possible biases

Lack of standardization in respiratory act/Valsalva amplitude.

### Suggested next research lines

Identification of eventual correlations between phasicity restoration and vein tract recanalization.

### Related statement in layman's term for public vein-lymphatic awareness

At the ultrasound, venous flow phasicity with the respiratory act can not exclude thrombosis. Ask your specialist for more information.

### Suggested pertinent extra readings

a) Denault AY, Aldred MP, Hammoud A, Zeng YH, Beaubien-Souligny W, Couture EJ, *et al.* Doppler interrogation of the femoral vein in the critically ill patient: The fastest potential acoustic window to diagnose right ventricular dysfunction? *Crit Care Explor* 2020;2:10.

b) Necas M. Duplex ultrasound in the assessment of lower extremity venous insufficiency. *Austral J Ultras Med* 2010;13:37-45.

c) Selis JE, Kadakia S. Venous Doppler sonography of the extremities: a window to pathology of the thorax, abdomen, and pelvis. *AJR Am J Roentgenol* 2009;193:1446-51.

d) Cozcolluela MR, Sarria L, Sanz L, Martinez-Berganza MT, de Vera JM, Bernal A, *et al.* Correlation of central venous pressure with Doppler waveform of the common femoral veins. *J Ultrasound Med* 2000;19:587-92.

## 7. Significance of venous cyclic flow in cardiovascular disease management

### Query used for the literature search

Pulsatile venous flow

### Main findings

Right heart pump failure leads to a venous dilation with transmission of the pressure wave also in the femoral district. A small amount of phasic retrograde flow in the common femoral vein can be considered physiological and it has been found in around 20% of healthy subjects.<sup>68</sup> Nevertheless, a pulsatile common femoral vein flow demonstrated correlations with right-sided heart failure, even if with a low sensitivity.<sup>69</sup> This data suggest the finding of such pulsatile flow must lead to a diagnostic suspect in the valuable sonographer, yet femoral vein scanning can not be considered as screening tool for right-sided heart failure.<sup>66</sup> High retrograde velocity peak recordings resulted to correlate with the degree of tricuspid regurgitation observed on echocardiography, yet an integrated patient investigation must be performed before coming to the final diagnosis.<sup>70</sup> The presence of pulsatile lower limb venous Doppler flow should alert the sonographer that a pathologic cardiac condition may be the culprit, especially in patients who have no such prior diagnosis.

### Analyzed literature possible biases

Possible confounding between respiratory and heart induced hemodynamic impact.

### *Suggested next research lines*

Evaluation of heart failure degree correlation with femoral vein hemodynamics synchronized with the respiratory function.

### *Related statement in layman's term for public vein-lymphatic awareness*

At the ultrasound, venous cyclic flow is not always a sign of cardiac disease, but proper clinical evaluation of the single case is mandatory.

### *Suggested pertinent extra readings*

a) Li X, Feng Y, Liu Y, Zhang F. Varicose Veins of the Lower Extremity Secondary to Tricuspid Regurgitation. *Ann Vasc Surg* 2019;60:477.e1-477.e6.

## **8. Ultrasound follow-up protocol after first deep venous thrombosis**

### *Query used for the literature search*

((ultrasound) AND (follow-up)) AND (venous thrombosis)

### *Main findings*

Clinical thrombotic risk individual assessment is of paramount importance both in the general clinical patient management and in the ultrasound surveillance strategy definition. Apart the globally accepted indication of not repeating the scanning if its result is not going to change the therapeutic management, internationally validated algorithms defining the ultrasound surveillance timeline are missing and a significant risk of under/over scanning exams is present, together with the related healthcare organizational and economic burden. Compression ultrasonography negative predictive value is over 97% indicating the need of repeated compression ultrasound testing within one week for a limited number of cases. Over 20% of patients develops a post-thrombotic syndrome and/or a thrombosis recurrence at one year. Proper risk stratification and related ultrasound surveillance timeline planning should be customized to the specific patient scenario.<sup>71</sup> Follow-up ultrasound assessment should be carefully planned in particular in patients with isolated calf vein thrombosis not undergoing anticoagulation and patients with recurrent signs and symptoms.<sup>72</sup> Diagnostic management of deep venous thrombosis surveillance in patients already affected by a previous episode might be complicated by the possible persistent abnormal D-dimer levels, residual obstruction and high clinical risk predictors. Age-adjusted D-dimer compared to a fix cut-off value demonstrated to add reliability to the thrombo-embolic episode eventual identification.<sup>73</sup> Further difficulties

in the best surveillance protocol definition have now been introduced by Covid pandemic which demonstrated to be associated with an increased deep venous thrombosis incidence. The need of ultrasound re-assessment has now to take this aspect into consideration as well.<sup>74</sup>

### *Analyzed literature possible biases*

Heterogenous study population and outcome measures in the evaluated surveillance protocols.

### *Suggested next research lines*

Head-to-head comparison of different surveillance protocols.

### *Related statement in layman's term for public vein-lymphatic awareness*

After a deep venous thrombosis event, a surveillance timeline should be tailored to the specific case.

### *Suggested pertinent extra readings*

a) Arabi YM, Burns KEA, Al-Hameed F, Alsolamy S, Almaani M, Mandourah Y, *et al.* Surveillance or no surveillance for deep venous thrombosis and outcomes of critically ill patients: A study protocol and statistical analysis plan. *Medicine (Baltimore)* 2018;97:e12258.

## **9. Intravenous ultrasound (IVUS) role in ilio-femoral venous stenting**

### *Query used for the literature search*

((("Stents/standards"[Mesh] OR "Stents/therapeutic use"[Mesh] )) AND "Ultrasonography, Interventional"[Mesh])

### *Main findings*

A recent literature review reported iliac vein compression in 24% of the asymptomatic population. Iliac vein compression has been also identified in up to 5% of the venous disease patients and in up to 49% of thrombosis cases.<sup>75</sup> IVUS demonstrated a superior sensitivity compared to venography in the assessment of treatable ilio-femoral vein stenosis, therefore becoming the gold standard for the characterization of this condition.<sup>76</sup> IVUS anatomical stenosis detection showed a correlation with the stenotic pressure gradient variation.<sup>77</sup> Yet, a detailed history and clinical evaluation of the specific patient case must be done before indicating a related iliac vein procedure. IVUS is also providing the benefit of a qualitative detailed identification of the post-thrombotic wall residual damage, such as fibrosis, mural thickening, spurs, and trabeculations. This feature is of paramount importance in the diagnostic work-up and

related treatment strategy identification, considering that the stenosis degree can not be taken into consideration alone as absolute value. Therefore, IVUS is an essential tool for guiding the procedure and the same treatment indication.<sup>78</sup> Before providing guidelines with high grade recommendations for IVUS use, further investigations including randomized comparative trials, are needed.

*Analyzed literature possible biases*

Interobserver variability analysis is needed.

*Suggested next research lines*

Mid- and long-term venous stenting patency improvement following IVUS use.

*Related statement in layman's term for public vein-lymphatic awareness*

IVUS can be extremely beneficial in iliac vein stenosis investigation and treatment planning.

*Suggested pertinent extra readings*

a) Chen ZH, Huang Y, Wang LP, Peng MY, Li C, Huang W. Preliminary study of hemodynamics of iliac venous compression syndrome using magnetic resonance imaging. *J Vasc Surg Venous Lymphat Disord* 2022;10:131-8.e3.

b) Montminy ML, Thomasson JD, Tanaka GJ, Lamanilao LM, Crim W, Raju S. A comparison between IVUS and venography in identifying key parameters essential for iliac vein stenting. *J Vasc Surg Venous Lymphat Disord* 2019;7:801-7.

c) Sang HF, Li JH, Du XL, Li WD, Lei FR, Yu XB, *et al.* Diagnosis and endovascular treatment of iliac venous compression syndrome. *Phlebology* 2019;34:40-51.

d) Gagne PJ, Gasparis A, Black S, Thorpe P, Passman M, Vedantham S, *et al.* Analysis of threshold stenosis by multiplanar venogram and IVUS examination for predicting clinical improvement after iliofemoral vein stenting in the VIDIO trial. *J Vasc Surg Venous Lymphat Disord* 2018;6:48-56.

**10. Ultrasound scanning protocol for lower limb lymphedema or lipedema**


*Query used for the literature search*

(lymphedema OR lipedema) AND ultrasound AND (lower limb)

*Main findings*

Ultrasound scanning of the lower limb lymphatic and fat tissue is feasible and potentially of great clinical importance

in lymphedema or lipedema patient management. Nevertheless, up to the authors knowledge, a validated protocol for ultrasound lower limb lymphedema and/or lipedema characterization has not yet been globally acquired. This is in line with the gaps already identified in the lymphedema guidelines field.<sup>79</sup> Potential ultrasound features have been reported for both lymphedema and lipedema. Lymphedema seems to be associated with increased skin thickness and dermal hypoechogenicity, particularly in the distal lower extremity, compared to lipedema or controls. Lipedema may be associated with increased thickness and hypoechogenicity of the subcutaneous fat. A cutoff value for ultrasound diagnosis of lipedema using thickness of the dermis and subcutaneous tissues has been recently published. In particular, the pre-tibial region showed good accuracy.<sup>80, 81</sup> These findings are preliminary and large investigations are needed to confirm them. An ultrasound



**2. VENOUS-LYMPHATIC DIAGNOSTICS**

Assessment of leg veins & lymphatic eventual impairment requires a deep knowledge of the topic. A detailed clinical evaluation must be followed by appropriate investigations. An extremely common exam is the ultrasound scanning: it presents great values in the diagnostic process, but it is also operator-dependent, thus making the expertise of the involved health-professional crucial.

The 10 below listed indications are supported by scientific evidence available for free, together with further educational material, at the herein reported website.

[www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)

**VENOUS-LYMPHATIC DIAGNOSTICS**

1. Echo-Doppler for lower limb venous disease detection must be performed with the patient in standing position. Pelvic sources of the disease must be excluded. Intravascular Ultrasound (IVUS) should always be taken into consideration for possibly treatable conditions.
2. Lower limb venous echo-Doppler report must include the deep, saphenous and superficial system findings.
3. The identification of a venous reflux or dilation at the ultrasound is not enough for indicating a treatment.
4. Superficial venous thrombosis identification at the ultrasound must always include both limbs and both the deep and superficial systems.
5. Ultrasound scanning for deep venous thrombosis detection must include a specialist visit and it should cover all the leg with assessments every 2 cm.
6. At the ultrasound, venous flow phasicity with the respiratory act can not exclude thrombosis. Ask your specialist for more information.
7. At the ultrasound, venous cyclic flow is not always a sign of cardiac disease, but proper clinical evaluation of the single case is mandatory.
8. After a deep venous thrombosis event, a surveillance timeline should be tailored to the specific case.
9. Intravenous ultrasound (IVUS) can be extremely beneficial in iliac vein stenosis investigation and treatment planning.
10. A leg ultrasound for venous drainage assessment should always include also an assessment of the eventually coexisting lymphedema and/or lipedema.

Figure 2.—Public vein-lymphatic awareness evidence-based statements in layman's terms regarding venous reflux appropriate detection by ultrasound.

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identification of different lymphedema stages has been proposed for the upper limb.<sup>82</sup> Similar data collection are encouraged in the lower limb lymphedema and lipedema patients. A recent review pointed out the potential role of ultrasound elastography in moderate-to-advanced lymphedema, specifying further studies are needed for early detection (Figure 2).<sup>83</sup>

#### *Analyzed literature possible biases*

Heterogenous or not specified lymphedema and lipedema stages in the assessed studies populations.

#### *Suggested next research lines*

Ultrasound characterization of the different lymphedema and lipedema stages.

#### *Related statement in layman's term for public vein-lymphatic awareness*

A leg ultrasound for venous drainage assessment should always also include an assessment of the eventually coexisting lymphedema and/or lipedema.

#### *Suggested pertinent extra readings*

a) Gasparis AP, Kim PS, Dean SM, Khilnani NM, Labropoulos N. Diagnostic approach to lower limb edema. *Phlebology* 2020;35:650-5.

b) Suehiro K, Morikage N, Ueda K, Samura M, Takeuchi Y, Nagase T, *et al.* Venous hemodynamics assessed with air plethysmography in legs with lymphedema. *Vasc Med* 2018;23:139-42.

c) Jensen MR, Simonsen L, Karlsmark T, Bülow J. Lymphoedema of the lower extremities--background, pathophysiology and diagnostic considerations. *Clin Physiol Funct Imaging* 2010;30:389-98.

### 3. Superficial venous procedures

#### 1. Indications to superficial venous treatment

##### *Query used for the literature search*

((((indication) AND (lower limb)) AND (chronic venous disease)) AND (treatment))

##### *Main findings*

Proper indication to lower limb superficial venous reflux treatment is of paramount importance to avoid overtreatment as well as undertreatment, for both intentional and unintentional clinical malpractice.<sup>84</sup> Venous reflux represents a risk factor for chronic venous disease development. Yet no significant difference in advanced CEAP clinical

class presentation was reported in the groups with and without reflux at the 13 years follow-up in the Edinburgh Study.<sup>55</sup> Therefore, anatomical reflux recurrence must not be the only outcome parameter and venous reflux presence cannot be considered as the only factor leading to treatment indication. This is clearly evident in the comparison between thermal tumescent and ultrasound guided foam sclerotherapy treatments: while the anatomical recurrence rate performance is in favor of a thermal tumescent approach, patient reported outcomes, morbidity and potentially cost-effectiveness might be in favor of ultrasound guided foam sclerotherapy.<sup>85</sup> The concept of “appropriateness” is pivotal in this context. A valuable 2020 publication reported appropriateness in the thermal tumescent ablation of the saphenous and of the incompetent tributaries whenever associated with chronic venous disease symptoms. To the contrary, the ablation of a not refluxing anterior accessory saphenous vein during an incompetent great saphenous vein treatment has been considered rarely appropriate. In general, asymptomatic patients should not be treated. Perforating veins should be treated only if in a symptomatic patient in advanced stages of the disease.<sup>50</sup> Saphenous sparing demonstrated to be a reliable alternative, potentially with a reduction in the reflux recurrence rate, but properly collected data are needed to lead to a strong recommendation.<sup>86</sup>

#### *Analyzed literature possible biases*

Main focus on anatomical reflux recurrence.

#### *Suggested next research lines*

- Focus on quality of life, patients reported outcomes, cost-effectiveness.
- Indication to treatment in asymptomatic patients.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Documented vein signs, symptoms and reflux must be present to indicate a superficial venous procedure.

#### *Suggested pertinent extra readings*

a) De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, *et al.* Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg* 2022;63:184-267.

b) Giancesini S, Obi A, Onida S, Baccellieri D, Bissacco D, Borsuk D, *et al.* Global guidelines trends and controversies in lower limb venous and lymphatic disease: Nar-

relative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics, 23-25 January 2019. *Phlebology* 2019;34(1 Suppl):4-66.

c) Chen C, Cai Y, Long X, Fan X, Yuan D, Yang Y, *et al.* Age is not a barrier to good outcomes following ambulatory high ligation and stripping for varicose veins: A prospective cohort study. *Medicine (Baltimore)* 2019;98(:e18085.

d) van der Velden SK, van den Bos RR, Pichot O, Nijsten T, De Maeseener M. Towards an individualized management strategy for patients with chronic venous disease: Results of a Delphi consensus. *Phlebology* 2018;33:492-9.

## 2. Surgical and thermal tumescent techniques for great saphenous vein reflux treatment

### Query used for the literature search

(great saphenous vein) AND (treatment)

### Main findings

International guidelines generally agree in indicating thermal tumescent techniques for great saphenous vein reflux treatment over traditional surgical stripping or other devices. Nevertheless, these conclusions are mainly following the evidence regarding the anatomical recurrence rate and mini-invasive performance, rather than taking into consideration also quality of life, patient reported outcomes and cost-efficacy.<sup>7</sup>A recent review showed the overlapping anatomical outcome in the comparison of stripping vs. thermal tumescent. Interestingly, these last ones were not superior and potentially significantly inferior to ultrasound guided foam sclerotherapy in terms of generic quality of life. Future recommendations are encouraged to take into consideration several factors apart just the reflux reappearance, such as patients' values and preferences, anatomic considerations and surgical expertise.<sup>87</sup> The Cochrane 2021 analysis on the specific treatment of the great saphenous vein pointed out that the conclusions are limited by the small number of data for the different head to head comparisons and the lack of homogeneity in outcome measures. All modalities showed overlapping technical success. No differences were reported in reflux recurrence, except for a possible long-term benefit of radiofrequency ablation compared to laser or stripping.<sup>88</sup> The importance of not relying just on vein caliber has been recently demonstrated by the analysis of the correlation between vein diameters, clinical severity and quality of life. Vein caliber is a poor predictor of health-related quality of life, therefore it should not be used as single parameter to indicate

eventual venous intervention.<sup>89</sup> Age over 65 demonstrated not to be a barrier for the good vein procedure outcome in terms of CEAP class, Venous Clinical Severity Score and Patient Reported Outcome scores.<sup>90</sup>

### Analyzed literature possible biases

Lack of homogeneous hemodynamic data collection and similar outcome measures.

### Suggested next research lines

Mid-long term homogenous outcome measures in homogenous hemodynamic study populations.

### Related statement in layman's term for public vein-lymphatic awareness

No significant difference in reflux reappearance risk is reported following surgical rather than endovenous thermal ablation of the great saphenous vein. No device has a whole performance better than the others.

### Suggested pertinent extra readings

a) Giannopoulos S, Rodriguez L, Chau M, Rodrigues D, Labropoulos N, Aziz F, *et al.* A Systematic Review About Outcomes of Percutaneous Treatment Modalities for Pathologic Saphenous And Perforating Veins. *J Vasc Surg Venous Lymphat Disord* 2022;10:1172-83.e5.

b) Cosin Sales O. Ultrasound-guided interventional radiology procedures on veins. *Radiologia (Engl Ed)* 2022;64:89-99.

c) Bellmunt-Montoya S, Escribano JM, Pantoja Bustillos PE, Tello-Díaz C, Martinez-Zapata MJ. CHIVA method for the treatment of chronic venous insufficiency. *Cochrane Database Syst Rev* 2021 Sep 30;9(9):CD009648.

d) Gianesini S, Occhionorelli S, Menegatti E, Malagoni AM, Tessari M, Zamboni P. Femoral vein valve incompetence as a risk factor for junctional recurrence. *Phlebology* 2018;33:206-12.

## 3. Surgical and thermal tumescent techniques for small saphenous vein reflux treatment

### Query used for the literature search

(small saphenous vein) AND (treatment)

### Main findings

The small saphenous vein incompetence accounts for around 15% of varicose veins cases. Its treatment requires proper hemodynamic and anatomic knowledge, considering also its proximity with neural structures.<sup>91</sup> Last Cochrane revision on the topic reported a better recurrence

rate following endovenous laser ablation rather than traditional surgery, while uncertain evidence was found in the comparison between ultrasound guided foam sclerotherapy and surgery.<sup>92</sup> Endovenous thermal ablation by both laser and radiofrequency showed potential usefulness also in redo cases, with no impact of age, gender, CEAP class, laterality, device, Body Mass Index, or vein diameter on the final outcome.<sup>93</sup> Preliminary data demonstrated safety and efficacy of a hybrid technique combining intra-operative intraluminal foam sclerotherapy injection and surgery.<sup>94</sup> Further investigations and properly designed comparative trials are needed in the small saphenous vein incompetence field. Such studies should include a longer than 5 years follow-up, together with multiple outcome measures, among which pain, quality of life and cost effectiveness.

#### *Analyzed literature possible biases*

Lack of homogeneity in anatomical and hemodynamic small saphenous vein characteristics.

#### *Suggested next research lines*

Longer than 5 y f up comparative trials involving homogeneous population.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Preliminary data suggest endovenous thermal ablation of the small saphenous vein leads to a smaller percentage of reflux reappearance compared to surgical ablation.

#### *Suggested pertinent extra readings*

a) Whiteley MS. Current Best Practice in the Management of Varicose Veins. *Clin Cosmet Investig Dermatol* 2022;6:567-83.

b) Giannopoulos S, Rodriguez L, Chau M, Rodrigues D, Labropoulos N, Aziz F, *et al.* A Systematic Review About Outcomes of Percutaneous Treatment Modalities for Pathologic Saphenous And Perforating Veins. *J Vasc Surg Venous Lymphat Disord* 2022;10:1172-83.e5.

c) Benfor B, Peden EK. A systematic review of management of superficial venous reflux in the setting of deep venous obstruction. *J Vasc Surg Venous Lymphat Disord* 2022;S2213-333X(22)00003-8.

d) Kheirelseid EAH, Crowe G, Sehgal R, Liakopoulos D, Bela H, Mulkern E, *et al.* Systematic review and meta-analysis of randomized controlled trials evaluating long-term outcomes of endovenous management of lower extremity varicose veins. *J Vasc Surg Venous Lymphat Disord* 2018 Mar;6(2):256-270.

## **4. Catheters injecting sclerotherapy anatomical and clinical performance**

### *Query used for the literature search*

((mechanochemical) OR (catheter)) AND (sclerotherapy)

### *Main findings*

A Cochrane revision on the topic confirmed endovenous laser and radiofrequency ablation as the most performing therapeutic options for saphenous vein reflux treatment.<sup>88</sup> Mechanical Occlusion Chemically Assisted ablation (MOCA) indicates the use of a specific catheter (Clarivein) endowed with endothelial cutting elements: the term MOCA should not be used to indicate procedures performed by other devices always aimed to cut the endothelial lining (for example, Flebogrif) but with different specifics and scientific literature support. MOCA seems to be promising, but further evidence on the effectiveness, reinterventions, costs and health-related quality of life are needed.<sup>95</sup> A 2022 network meta-analysis showed the lowest risk of procedural failure at 6 weeks follow-up following cyanoacrylate ablation, while in the long follow-up, CHIVA saphenous sparing option and traditional surgery demonstrated the best recurrence-free performance. Mechano-chemical ablation was included in the search, but it resulted to be not competitive against surgery or endovenous laser/radiofrequency.<sup>96</sup> A dedicated randomized comparative trial showed a significantly better reflux recurrence rate following the use of endovenous laser ablation vs. MOCA, yet no significant differences in Venous Clinical Severity score and Aberdeen Varicose Veins Questionnaire.<sup>97</sup> A 2021 revision on Flebogrif reported just 3 studies with a maximum of 12 months follow-up and a moderate methodology quality. The same revision recommended properly conducted data collection and head-to-head comparison before recommending the use of the device.<sup>98</sup> In 2020, a meta-analysis dedicated to catheter directed sclerotherapy (without endothelial cutting elements), showed better ablation rates compared to direct injection sclerotherapy. Yet more data are needed to allow inclusion of this technical solution in the large revisions dedicated to the topic.<sup>99</sup>

### *Analyzed literature possible biases*

Lack of homogeneity in the study populations hemodynamics and short f up.

### *Suggested next research lines*

Flebogrif longer than 12 months head to head comparison with Clarivein.

*Related statement in layman's term for public vein-lymphatic awareness*

Catheters injecting sclerotherapy while incising the saphenous vein demonstrated to be safe (Clarivein, Flebogrif) and inferior to thermal ablation in venous reflux reappearance, but not inferior in some clinical outcomes (Clarivein).

*Suggested pertinent extra readings*

a) Cosin Sales O. Ultrasound-guided interventional radiology procedures on veins. Radiologia (Engl Ed) 2022;64:89-99.

b) Whing J, Nandhra S, Nesbitt C, Stansby G. Interventions for great saphenous vein incompetence. Cochrane Database Syst Rev 2021;8(8):CD005624.

**5. Steam ablation clinical and anatomical performance**

*Query used for the literature search*

((steam) AND (vein))

*Main findings*

In 2014 a randomized comparative trial demonstrated not inferiority of endovenous steam ablation versus endovenous laser ablation in reflux recurrence. Aberdeen Varicose Vein Questionnaire, EQ-5DTM and EQ-VAS improved similarly in the two groups. It must be noted that the comparison had a follow-up of just 1 year.<sup>100</sup> A more recent publication confirmed the satisfactory performance of steam ablation in patient's symptoms and venous hemodynamics, but always with a 1 year follow-up only.<sup>101</sup> Up to our knowledge literature reporting longer than 1 year follow-up was reported only in languages different from English. A Dutch publication reported a 5 year follow-up and a Norwegian one a comparative trial against stripping.<sup>102, 103</sup> Properly collected long term data are needed before including steam ablation in related guidelines with high recommendation grade.<sup>88</sup>

*Analyzed literature possible biases*

Short follow-up data and not English literature for longer follow-up.

*Suggested next research lines*

Longer than 5 years follow-up comparative data.

*Related statement in layman's term for public vein-lymphatic awareness*

Ablation of the great saphenous vein by steam is safe but more scientific data are needed before recommending it in place of laser or radiofrequency treatment.

*Suggested pertinent extra readings*

a) Whiteley MS. Glue, steam and Clarivein--Best practice techniques and evidence. Phlebology 2015;30(2 Suppl):24-8.

b) Thomis S, Verbrugghe P, Milleret R, Verbeken E, Fournau I, Herijgers P. Steam ablation versus radiofrequency and laser ablation: an in vivo histological comparative trial. Eur J Vasc Endovasc Surg 2013;46:378-82.

**6. Glue ablation clinical and anatomical performance**

*Query used for the literature search*

(glue) and (vein)

*Main findings*

A 2021 meta-analysis reported no statistical difference in closure rates between cyanoacrylate ablation and endovenous thermal ablation by laser or radiofrequency. Symptoms were controlled similarly by the different techniques. Cyanoacrylate group showed less ecchymosis than radiofrequency and a significantly lower incidence ecchymosis, phlebitis and paresthesia compared to endovenous laser.<sup>104</sup> It must be specified data at 5 years follow-up are related only to a specific glue (Venaseal), following the randomized trial in comparison with radiofrequency ablation.<sup>105</sup> In a 2020 network meta-analysis, at 6 months follow-up, Venaseal demonstrated to be competitive against traditional surgery, laser, radiofrequency and MOCA in terms of anatomical recurrence, post-operative pain and adverse events.<sup>106</sup> Cost-effectiveness resulted not competitive compared to laser and radiofrequency ablation according to the United Kingdom health system analysis.<sup>95</sup> Venaseal demonstrated safety and efficacy also in ulcer patients reflux treatment, with potential benefit compared to saphenous reflux suppression by radiofrequency.<sup>107</sup> It must be clearly stated to the patient that the procedure leads to the deposition of a foreign body and that more than 2% of cases might developed related complications.<sup>108</sup>

*Analyzed literature possible biases*

Heterogenous study populations among different types of glue.

*Suggested next research lines*

Head-to-head comparison of different glue types in clinical, hemodynamic and patient reported outcomes.

*Related statement in layman's term for public vein-lymphatic awareness*

Ablation of the great saphenous vein by glue has a clinical result not inferior to radiofrequency (Venaseal) at 5 years

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and not inferior to laser at 2 years (Venablock). The patient must be informed the glue will remain as foreign body. Different glues have different scientific validation and this must be clearly stated.

*Suggested pertinent extra readings*

a) O'Banion LA, Reynolds KB, Kochubey M, Cutler B, Tefera EA, Dirks R, *et al.* A comparison of cyanoacrylate glue and radiofrequency ablation techniques in the treatment of superficial venous reflux in CEAP 6 patients. *J Vasc Surg Venous Lymphat Disord* 2021;9:1215-21.

b) Chan SSJ, Chan YC, Walsh SR, Chong TT, Choke ETC, Tiwari A, *et al.* Endovenous cyanoacrylate ablation for chronic venous insufficiency and varicose veins among Asians. *Ann Acad Med Singap* 2021;50:241-9.

c) Dimech AP, Cassar K. Efficacy of Cyanoacrylate Glue Ablation of Primary Truncal Varicose Veins Compared to Existing Endovenous Techniques: A Systematic Review of the Literature. *Surg J (N Y)* 2020;6:e77-e86.

d) Hartmann K. Endovenous (minimally invasive) procedures for treatment of varicose veins : The gentle and effective alternative to high ligation and stripping operations. *Hautarzt* 2020;71(Suppl 2):67-73.

e) Parsi K, Roberts S, Kang M, Benson S, Baker L, Berman I, *et al.* Cyanoacrylate closure for peripheral veins: Consensus document of the Australasian College of Phlebology. *Phlebology* 2020;35:153-75.

f) Radak D, Djukic N, Neskovic M. Cyanoacrylate Embolization: A Novelty in the Field of Varicose Veins Surgery. *Ann Vasc Surg* 2019;55:285-91.

g) Epstein D, Onida S, Bootun R, Ortega-Ortega M, Davies AH. Cost-Effectiveness of Current and Emerging Treatments of Varicose Veins. *Value Health* 2018;21:911-20.

h) Bissacco D, Stegher S, Calliari FM, Viani MP. Saphenous vein ablation with a new cyanoacrylate glue device: a systematic review on 1000 cases. *Minim Invasive Ther Allied Technol* 2019;28:6-14.

**7. Saphenous sparing**

*Query used for the literature search*

((saphenous sparing) OR (chiva)) OR (asval)

*Main findings*

Lower limb chronic venous disease can be treated by different procedural approaches. A fundamental distinction must be made between different techniques and strategies. While the technique indicates the selected therapeutic instruments, the strategy refers to the hemodynamic

plan designed to restore a physiological venous drainage. Ablative strategy is aimed to remove the vein affected by the reflux, while saphenous sparing approaches are aimed to convert the reflux in an anti-inflammatory flow by closing the leaking points of the system (so called "CHIVA")<sup>109</sup> or by ablating only the incompetent tributaries (so called "ASVAL").<sup>110</sup> A Cochrane reported that CHIVA may make little or no difference compared to traditional surgery and endovenous thermal ablation, yet the conclusions reported also the need to increase the dedicated research as the evidence so far is of low certainty.<sup>86</sup> A recent meta-analysis supported CHIVA as it seemed to have superior clinical benefits on long-term efficacy for treating varicose veins.<sup>111</sup> A significant literature is also in support of ASVAL, but properly randomized trials are needed before releasing a high grade recommendation.<sup>110</sup> Endovenous laser and radiofrequency demonstrated to be safe and effective in the short term follow-up for segmental great saphenous vein treatment aimed to suppress the reflux without ablating all the refluxing vessel.<sup>112</sup> Significant expertise in hemodynamics and proper patient selection is mandatory before performing saphenous sparing procedures.<sup>113</sup>

*Analyzed literature possible biases*

Heterogeneous study populations in terms of hemodynamics patterns.

*Suggested next research lines*

Multi-center randomized comparative trials testing saphenous sparing vs. thermal tumescent in homogeneous populations.

*Related statement in layman's term for public vein-lymphatic awareness*

In expert hands, procedures not eliminating the saphenous vein can be a valid alternative to procedures aimed to remove the saphenous trunk.

*Suggested pertinent extra readings*

a) Alozai T, Huizing E, Schreve MA, Mooij MC, van Vlijmen CJ, Wisselink W, *et al.* A systematic review and meta-analysis of treatment modalities for anterior accessory saphenous vein insufficiency. *Phlebology* 2022;37:165-79.

b) González Cañas E, Florit López S, Vilagut RV, Guevara-Noriega KA, Santos Espí M, Rios J, *et al.* A randomized controlled noninferiority trial comparing radiofrequency with stripping and conservative hemodynamic cure for venous insufficiency technique for insufficiency

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of the great saphenous vein. *J Vasc Surg Venous Lymphat Disord* 2021;9:101-2.

c) Parés JO, Juan J, Tellez R, Mata A, Moreno C, Quer FX, *et al.* Varicose vein surgery: stripping versus the CHIVA method: a randomized controlled trial. *Ann Surg* 2010;251:624-31.

d) Carandina S, Mari C, De Palma M, Marcellino MG, Cisno C, Legnaro A, *et al.* Varicose vein stripping vs. haemodynamic correction (CHIVA): a long term randomised trial. *Eur J Vasc Endovasc Surg* 2008;35:230-7.

e) Zamboni P, Cisno C, Marchetti F, Mazza P, Fogato L, Carandina S, *et al.* Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. *Eur J Vasc Endovasc Surg* 2003;25:313-8.

## 8. Superficial venous disease periprocedural thrombotic risk management

### Query used for the literature search

((thrombosis) AND (varicose veins)) AND (procedure)

### Main findings

The thrombotic risk associated with varicose veins procedures has been reported to be low after endovenous thermal ablation (<2%). Nevertheless, limited data are available on non-thermal non-tumescent devices use and thrombotic complications have been documented in more than 6% of cases.<sup>114</sup> At the same time, caution in such risk management was previously requested by data showing up to 16% of thrombosis following endovenous thermal ablation.<sup>115</sup> Properly assessing the thrombotic risk of both the patient and of the procedure is of paramount importance. Unfortunately, data allowing proper scoring of the different thrombotic risk along the several chronic venous disease stages are still missing, as well as for the specific risk stratification of the different procedural options. An extended course of thromboprophylaxis demonstrated to reduce the risk of developing deep venous thrombosis compared to a short course. However, the available data did not stratify on the patients thrombotic risk.<sup>116</sup> Endothermal Heat Induced Thrombosis incidence has been documented in very rare cases (0.11% for EHIT type 3, 0.013% for EHIT type 4, 0.063% for other thrombosis),<sup>117</sup> leading to questioning the real necessity of routine post-operative ultrasound surveillance.<sup>118</sup> In conclusion, until larger randomized comparative trials won't be published on the topic, maximum care in not underestimating the thrombotic risk of superficial venous procedures must be paid, focusing on properly assessing the risk of both the patient and of the procedure in an individualized way.

### Analyzed literature possible biases

Different outcome measures (clinical, ultrasound, lab) for thrombosis detection.

### Suggested next research lines

Multi-center head-to-head thromboprophylaxis schemes comparison, with homogeneous thrombosis detection outcome measures.

### Related statement in layman's term for public vein-lymphatic awareness

All venous procedures bring a small but potentially significant thrombo-embolic risk: individual risk and related prophylaxis must be performed by an expert physician.

### Suggested pertinent extra readings

a) Boyle E, Reid J, O'Donnell M, Harkin D, Badger S. Thromboprophylaxis for varicose vein procedures - A national survey. *Phlebology* 2019;34:598-603.

b) Sweetland S, Green J, Liu B, Berrington de González A, Canonico M, Reeves G, *et al.* Duration and magnitude of the postoperative risk of venous thromboembolism in middle aged women: prospective cohort study. *BMJ* 2009;339:b4583.

## 9. Superficial venous disease periprocedural graduated compression indication

### Query used for the literature search

((stockings) AND (graduated compression)) AND (venous)) AND (procedure)

### Main findings

Graduated compression use after lower limb veins procedures is generally considered a fundamental practice. Yet, literature and related guidelines recommendations have shown a tendency toward heterogeneity and uncertainty regarding the real benefit brought by the same compression in this context. In 2019 a joint societies document focused on the use of compression as best practice, leaving to the physicians the individual case benefit evaluation. This document delivered a 2C recommendation for compression use after surgical or endothermal saphenous ablation.<sup>119</sup> Interestingly, a couple of years later, another group gave a IA indication to compression after stripping and/or extensive phlebectomies and just stated that compression should be considered following sclerotherapy or thermal saphenous ablation.<sup>120</sup> Up to our knowledge, the literature assessing the eventual benefit of compression after a procedure has not yet produced a significant amount of data

coming from clinically and hemodynamically and demographically homogeneous populations, undergoing always comparable procedures, therefore a proper meta-analysis is not yet feasible.<sup>121</sup> Moreover, it should be noted that compression aim is not just thromboprophylaxis, therefore also its impact on recovery time, quality of life, edema and hematoma control should be taken into consideration, together with several other aspects, among which the cost-effectiveness.<sup>122</sup> Expert physicians should always assess the single case benefit and the related risk/benefit ratio, knowing that compression demonstrated its high safety profile, as long as prescribed by expert professionals.

*Analyzed literature possible biases*

Lack of homogenous data collection in terms of outcome measures, procedure type and intensity (for example segmental vs. extensive ablation).

*Suggested next research lines*

Multicenter randomized comparative trials assessing objective clinical and patient reported outcomes after a vein procedure with/without compression.

*Related statement in layman's term for public vein-lymphatic awareness*

Right after a venous procedure, certified graduated compression stockings can be beneficial, as long as prescribed by an expert health professional.

*Suggested pertinent extra readings*

- a) Tan MKH, Salim S, Onida S, Davies AH. Postsclerotherapy compression: A systematic review. *J Vasc Surg Venous Lymphat Disord* 2021;9:264-74.
- b) Shalhoub J, Lawton R, Hudson J, Baker C, Bradbury A, Dhillon K, *et al.* Graduated compression stockings as adjuvant to pharmaco-thromboprophylaxis in elective surgical patients (GAPS study): randomised controlled trial. *BMJ* 2020;369:m1309.
- c) Suna K, Herrmann E, Kröger K, Schmandra T, Müller E, Hanisch E, *et al.* Graduated compression stockings in the prevention of postoperative pulmonary embolism. A propensity-matched retrospective case-control study of 24,273 patients. *Ann Med Surg* 2020;56:203-10.

**10. Superficial venous disease procedures complications incidence & management**

*Query used for the literature search*

((complications) AND (superficial venous)) AND (procedure)

*Main findings*

Both superficial venous surgery and endovenous procedures demonstrated to be safe and associated with a low rate of complications, as long as performed by expert professionals.

All the interventions share the following possible side effects: allergy to the eventual anesthetic/ablation drug, infection, bleeding, nerve and lymphatic damage, arterio-venous-lymphatic fistula, thrombosis, pain, skin ulceration/burn, bruises, hematoma, catheter/fiber fracture and migration. The use of glue can lead to granuloma and to foreign body migration. Informing patients about the foreign body nature of the glue assisted ablation is mandatory.<sup>88</sup> Catheters used for mechano-chemical ablation can get stuck into the vein, forcing to a retrograde inversion stripping.<sup>123</sup> In the short term, postprocedural pain has been reported to be potentially lower following non-thermal non-tumescent. These last ones showed also lower rates of ecchymo-

**3. VENOUS PROCEDURES**

Industrialized countries population is presenting a constantly increasing mean age, sedentarism and tendency to obesity. These facts parallel the equally constantly increasing demand for leg chronic venous disease interventional treatment. Different techniques can be used: **surgery**, **endovenous thermal ablation** (Laser, Radiofrequency, Steam), **endovenous non thermal ablation** (glue, foam-assisted non-thermal ablation), **sclerotherapy** (described in an entirely dedicated section of this document). Two main strategies can be applied: ablation of the diseased vein or restoration of a normal flow by closure of selective diseased vein segments. Evidence-based facts on the topic are reported below, with insights available at [www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)



**SUPERFICIAL VENOUS PROCEDURES**

1. Documented vein signs, symptoms & reflux must be present to indicate a superficial venous procedure.
2. No significant difference in reflux reappearance risk is reported following surgical rather than endovenous thermal ablation of the great saphenous vein. No device has a whole performance better than the others.
3. Preliminary data suggest endovenous thermal ablation of the small saphenous vein leads to a smaller percentage of reflux reappearance compared to surgical ablation.
4. Catheters injecting sclerotherapy while incising the saphenous vein demonstrated to be safe (Clarivein®, Flebogrif®) and inferior to thermal ablation in venous reflux reappearance, but not inferior in some clinical outcomes (Clarivein®).
5. Ablation of the great saphenous vein by steam is safe but more scientific data are needed before recommending it in place of laser or radiofrequency treatment.
6. Ablation of the great saphenous vein by glue has a clinical result not inferior to radiofrequency (Venaseal®) at 5 years and not inferior to laser at 2 years (Venablock®). The patient must be informed the glue will remain as foreign body. Different glues have different scientific validation and this must be clearly stated.
7. In expert hands, procedures not eliminating the saphenous vein can be a valid alternative to procedures aimed to remove the saphenous trunk.
8. All venous procedures bring a small but potentially significant thrombo-embolic risk: individual risk and related prophylaxis must be performed by an expert physician.
9. Right after a venous procedure, certified graduated compression stockings can be beneficial, as long as prescribed by an expert health professional.
10. Superficial venous disease procedures are safe, yet significant complications can happen, therefore only expert physicians should be involved in their management.

Figure 3.—Public vein-lymphatic awareness evidence-based statements in layman's terms regarding superficial venous procedures.

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sis, while no difference was identified in paresthesia, skin pigmentation and thrombosis.<sup>124</sup> The reported thrombotic complications of endovenous heat induced thrombosis and deep venous thrombosis associated with thermal tumescent techniques are low (<2%). A dedicated review recently suggested non-thermal non-tumescent approaches might lead to a higher thrombotic complication rate (up to 6%).<sup>114</sup> Nevertheless, properly powered trials with long follow-up observation are needed on the topic (Figure 3).

*Analyzed literature possible biases*

Lack of head-to-head safety profile comparison among different techniques in homogeneous study population.

*Suggested next research lines*

Real world data on venous procedure complications.

*Related statement in layman's term for public vein-lymphatic awareness*

Superficial venous disease procedures are safe, yet significant complications can happen, therefore only expert physicians should be involved in their management.

*Suggested pertinent extra readings*

a) Eysenbach LM, Koo KSH, Monroe EJ, Reis J, Perkins JA, Shivaram GM. Migration of n-BCA glue as a complication of venous malformation treatment in children. *Radiol Case Rep* 2021;16:3526-33.

b) Parsi K, Kang M, Yang A, *et al.* Granuloma formation following cyanoacrylate glue injection in peripheral veins and arteriovenous malformation. *Phlebology* 2020;35:115-23.

c) Lun Y, Shen S, Wu X, *et al.* Laser fiber migration into the pelvic cavity: A rare complication of endovenous laser ablation. *Phlebology* 2015;30:641-3.

d) Dexter D, Kabnick L, Berland T, *et al.* Complications of endovenous lasers. *Phlebology* 2012;27 Suppl 1:40-5.

**4. Deep venous and malformations**

**1. Deep venous pathophysiology**

*Query used for the literature search*

((deep venous) AND (pathophysiology)) AND (lower limb)

*Main findings*

Lower limb deep venous insufficiency can be caused by flow obstruction and/or by valve incompetence. In the first case, an intraluminal thrombosis or external compression

(tumor, anatomic variants, aneurysms, etc) can be identified as cause of deep reflux. This latter can also be the consequence of the vein drainage volume overload by central causes (heart failure, for example) and/or of the valve structure compromise by previous insults (thrombotic inflammation, scarring and adhesions). Patients affected by an active or healed leg venous ulcer showed an ilio-caval obstruction in up to 37% of cases. Risk factors independently associated with a >80% obstruction are female gender, previous deep venous thrombosis and deep reflux.<sup>125</sup> Prompt identification and proper management of deep venous thrombosis is of paramount importance to decrease the post-thrombotic syndrome risk, which is expected in 20% to 50% of patients, with 5% to 10% developing the most advanced stage, including ulceration. Principal risk factors for post-thrombotic syndrome are extensive thrombosis, recurrent ipsilateral events, persistent leg symptoms for more than 1 month after the diagnosis, obesity, and advanced age.<sup>36</sup> In the population affected by superficial venous reflux, a deep reflux has been reported up to 40% of cases and mainly associated with obesity. Gender predominance has been reported in a heterogeneous way in the literature.<sup>126</sup> The main localization of deep reflux in patients with primary superficial venous insufficiency is in the common femoral vein and it is of short duration: a possible explanation of the benefit of superficial reflux abolition on deep venous incompetence restoration.<sup>127</sup>

*Analyzed literature possible biases*

Methodology and study population heterogeneity in epidemiology assessment.

*Suggested next research lines*

- Multiracial deep venous disease burden assessment.
- Obesity induced deep venous hypertension management.

*Related statement in layman's term for public vein-lymphatic awareness*

Not only the superficial venous system must be assessed: deep veins of the leg can present a reflux because of spontaneous or post-thrombotic or post-trauma valve damage and/or vein obstruction.

*Suggested pertinent extra readings*

a) Luo P, Xu J, Cheng S, Xu K, Xu K, Jing W, Zhang F, *et al.* Large-scale genetic correlation scanning and causal association between deep vein thrombosis and human blood metabolites. *Sci Rep* 2022;12:7888.

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b) Benfor B, Peden EK. A systematic review of management of superficial venous reflux in the setting of deep venous obstruction. *J Vasc Surg Venous Lymphat Disord* 2022 Jan 20;S2213-333X(22)00003-8

c) Navarrete S, Solar C, Tapia R, Pereira J, Fuentes E, Palomo I. Pathophysiology of deep vein thrombosis. *Clin Exp Med* 2022. [Epub ahead of print].

d) Radaideh Q, Patel NM, Shammam NW. Iliac vein compression: epidemiology, diagnosis and treatment. *Vasc Health Risk Manag* 2019;15:115-22.

e) Bradbury A, Evans CJ, Allan P, Lee AJ, Ruckley CV, Fowkes FG. The relationship between lower limb symptoms and superficial and deep venous reflux on duplex ultrasonography: The Edinburgh Vein Study. *J Vasc Surg* 2000;32:921-31.

## 2. Superficial venous insufficiency role in deep venous disease

### Query used for the literature search

((superficial) AND (deep)) AND (reflux) AND (abolition))

### Main findings

Great and small saphenous system reflux suppression demonstrated to be safe and potentially effective also in eventually coexisting deep venous reflux management.<sup>128</sup> A recent analysis reported successful deep reflux suppression in about a third of patients, particularly in case of segmental rather than axial deep drainage compromise.<sup>129</sup> Popliteal or femoral reflux velocities lower than 10 cm/sec have been found to be associated with a more pronounced improvement in both the venous filling index and the venous clinical severity score following superficial venous reflux treatment.<sup>130</sup> It must be noted that cases affected by deep venous reflux presented a significant rate of complications following superficial venous ablation in a dedicated publication, therefore proper patient selection must be performed before indicating the treatment.<sup>131</sup> Preliminary evidence suggests that superficial venous reflux ablation is safe also in case of concurrent deep venous obstruction, eventually combined with resolution of the same drainage impediment. Nevertheless, additional investigations are needed to confirm safety and efficacy of superficial venous reflux suppression in relieving signs and symptoms associated with the deep venous obstruction.<sup>132</sup>

### Analyzed literature possible biases

- Heterogeneity in the study populations.
- Short follow-up assessment.

### Suggested next research lines

- Deep venous treatment timing after/before superficial venous reflux suppression.
- Potential mechanisms for the development of venous insufficiency and deep venous disease due to hypoxia and apoptosis of the vein wall.

### Related statement in layman's term for public vein-lymphatic awareness

Patients with superficial venous insufficiency and deep venous reflux might be candidate for superficial venous treatment, yet an expert evaluation of the specific case is needed.

### Suggested pertinent extra readings

a) Köksoy C, Bahçecioğlu İB, Çetinkaya ÖA, Akkoca M. Iliocaval outflow obstruction in patients with venous ulcers in a small comparison study between patients with primary varicose veins and chronic deep vein disease. *J Vasc Surg Venous Lymphat Disord* 2021;9:703-11.

b) Hong KP, Kim DK. The Effect of Saphenous Vein Ablation on Combined Segmental Popliteal Vein Reflux. *Korean J Thorac Cardiovasc Surg* 2018;51(5):338-43.

c) Hirmerova J, Seidlerova J, Subrt I. Deep vein thrombosis and/or pulmonary embolism concurrent with superficial vein thrombosis of the legs: cross-sectional single center study of prevalence and risk factors. *Int Angiol* 2013;32(4):410-6.

d) MacKenzie RK, Allan PL, Ruckley CV, Bradbury AW. The effect of long saphenous vein stripping on deep venous reflux. *Eur J Vasc Endovasc Surg* 2004;28:104-7.

## 3. Iliac venous stenosis proper management

### Query used for the literature search

(iliac vein) AND (stenosis)

### Main findings

Iliac vein tract is the principal route of venous drainage from the lower limbs. Yet, a globally accepted definition of “hemodynamically significant iliac vein stenosis” is still missing and investigations focused on direct pressure measurements remain inconclusive. Up to 66% of the general population may have an asymptomatic non-thrombotic iliac vein lesion, therefore proper indication to treatment is of paramount importance to avoid under/over treatment. Asymptomatic patients without severe signs of venous hypertension should not be treated invasively. Only cases showing a life-affecting condition should be addressed to the stenosis dilation and eventual stenting.<sup>133</sup>

A detailed diagnostic work up should be performed by dedicated centers, including clinical evaluation, duplex ultrasonography, computed tomography and/or magnetic resonance venography. Intraoperatively use of IVUS demonstrated superiority in relation to venography. IVUS determines the degree of stenosis detecting the presence and characteristics of intraluminal obstructions, of the wall and of eventual residual thrombus fragments. It also determines the segment to position the stent at best, based also on the inflow and outflow. Venography demonstrated to underestimate the obstruction degree in approximately 30% of cases, failing to identify greater than 50% stenosis in 25% of patients.<sup>134</sup> Venous occlusion plethysmography have been proposed as a possible tool for quantifying the iliac stenosis impact and the possible stenting benefit, but preliminary data are not supporting its use.<sup>135</sup> Once the indication to treatment is given, the main option is endovascular by angioplasty and eventual stenting. Significant data are missing in the head-to-head comparison between angioplasty and stenting, but angioplasty alone is usually not considered sufficient to overcome the elastic recoil of the stenosis. Open surgery procedures did not show outcomes leading to high recommendation grades in the guidelines and must be performed, if and whenever necessary, only in highly specialized centers, taking into consideration that up to 40% complication rate has been reported. Conservative management by graduated compression and adapted physical exercise should always be taken into consideration. Whatever treatment strategy is indicated, close follow-up is part of the management plan.<sup>120</sup>

#### Analyzed literature possible biases

- Lack of homogeneous stenosis definition.
- Lack of objective outcome measures to compare the results.

#### Suggested next research lines

- Chronic venous obstruction management in obese patients before severe weight reduction attempt.
- Head-to-head appropriate conservative versus invasive chronic venous obstruction management.

#### Related statement in layman's term for public vein-lymphatic awareness

A narrowing of the iliac vein is present in more than 50% of the population: a caliber reduction alone is not an indication to treatment *per se*. Only specialized centers should treat iliac vein stenosis and only after careful evaluation of the risk and benefit.

#### Suggested pertinent extra readings

a) Saleem T, Raju S. An overview of in-stent restenosis in iliofemoral venous stents. *J Vasc Surg Venous Lymphat Disord* 2022;10:492-503.e2.

b) Rossi FH, Rodrigues TO, Izukawa NM, *et al.* Best practices in diagnosis and treatment of chronic iliac vein obstruction. *J Vasc Bras* 2020;19:e20190134.

c) Kutsenko O, McColgan Y, Salazar G. Iliac Vein Stenosis: Is the Data Strong Enough for Stenting in the Young Pelvic Venous Disorders (PeVD) Population? *Tech Vasc Interv Radiol* 2021;24:100733.

d) Saleem T, Raju S. Comparison of IVUS and multi-dimensional contrast imaging modalities for characterization of chronic occlusive iliofemoral venous disease: A systematic review. *J Vasc Surg Venous Lymphat Disord* 2021;9:1545-56.e2.

#### 4. Ilio-femoral venous stenting indications

##### Query used for the literature search

((iliac vein) AND (stenting)) AND (indication)

##### Main findings

Often iliac vein stenosis studies are not reporting a detailed hemodynamic characterization and they are often including patients previously affected by deep venous thrombosis. Moreover, the assessment is usually done just in the supine position, potentially altering the stenosis degree.

The obstruction must be evaluated into clinical context in order to provide proper indication to stenting.<sup>136</sup> Advanced chronic venous disease signs and symptoms must be documented before indicating the treatment, avoiding procedures just for anatomical stenosis finding. In the clinical scenario, also pelvic venous disorder manifestations must be taken into account as possible indication to treatment. Among such symptoms, chronic pelvic pain, perineal heaviness, urinary urgency, postcoital pain, and vulvar or superficial non-saphenous veins varicosities must be included. In this context, iliac vein treatment can be taken into consideration together with ovarian vein embolization and/ or direct embolization of the perineal varicosities. A paucity of evidence-based data has been produced so far, therefore further investigations are needed before providing high grade recommendations. A 6 months follow-up double-blind randomized clinical trial compared medical treatment (aminaphone, 20-30 mmHg graduated compression stockings and bandaging) vs. iliac vein stenting in 207 severe chronic venous disease patients, reporting superiority of the intervention in pain, venous clinical se-

verity score and quality of life. Further studies including properly developed pharmacological, graduated compression and exercise protocols head-to-head comparison with stenting are needed, in particular with a mid-long term follow-up.<sup>133</sup> Rizvi *et al.* reported a 98.6% of stent patency at two years in non-thrombotic iliac vein lesions.<sup>137</sup> Yet, in the 12 months follow-up, complications have been reported in up to 39% of cases, therefore pointing out the need of further proper investigations on the topic and of only dedicated centers management for this kind of procedure.<sup>138</sup>

#### *Analyzed literature possible biases*

Heterogenous study populations in short follow-up analysis.

#### *Suggested next research lines*

- Iliac vein stenosis stenting indication with/without IVUS.
- Qualitative and quantitative assessment of the vein inflow.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Ilio-femoral venous stenting for obstruction must be performed after specialist careful evaluation and only in patients affected by severe compromise.

#### *Suggested pertinent extra readings*

a) Taha MAH, Busuttill A, Bootun R, Thabet BAH, Badawy AEH, Hassan HA, *et al.* A clinical guide to deep venous stenting for chronic iliofemoral venous obstruction. *J Vasc Surg Venous Lymphat Disord* 2022;10:258-66.e1.

b) Kutsenko O, McColgan Y, Salazar G. Iliac Vein Stenosis: Is the Data Strong Enough for Stenting in the Young Pelvic Venous Disorders (PeVD) Population? *Tech Vasc Interv Radiol* 2021;24:100733.

c) Rodrigues LDS, Bertanha M, El Dib R. Association between deep vein thrombosis and stent patency in symptomatic iliac vein compression syndrome: Systematic review and meta-analysis. *J Vasc Surg Venous Lymphat Disord* 2021;9:275-84.

d) Hansrani V, Moughal S, Elmetwally A. A review into the management of May-Thurner syndrome in adolescents. *J Vasc Surg Venous Lymphat Disord* 2020;8:1104-10.

### **5. Deep venous reflux management**

#### *Query used for the literature search*

(deep venous) AND (reflux)

#### *Main findings*

Deep venous reflux definition is not globally agreed in the scientific community. In the same way, the reflux extent and hemodynamic impairment to make it considered significant have not yet been univocally characterized. Confounding factors such as the different definitions of “segmental” reflux and the frequent coexistence of superficial venous reflux make this task challenging. Deep reflux extended all the way to the knee and calf demonstrated to be associated with a severe compromise of the lower limb drainage, independently by the eventual superficial venous reflux coexistence. A system to classify deep venous reflux severity not based just on the anatomical location is needed.<sup>139</sup> Several options have been proposed for deep venous reflux management, among which ligation of deep veins, transposition, transplantation, primary valve repair, autogenous and artificial valve substitutes. The reflux primary or secondary etiology, patient’s specific preference and the surgical skills determine the technical choice that, whatever it is, so far and up to our knowledge, produced heterogeneous results, with a limited number of treated cases and not significantly long follow-up. Along the years many attempts to use a biologic or artificial valve has been reported, nevertheless the outcome remains underpowered in number of treated cases and followed up for a short time.<sup>140</sup> In this context proper conservative measures remain of pivotal importance for deep venous reflux. Among these, graduated compression, whenever appropriately prescribed, demonstrated objective benefit in venous hypertension reduction.<sup>141</sup> Further investigations are needed to identify the most effective protocol in deep venous reflux management.

#### *Analyzed literature possible biases*

Few data regarding isolated deep reflux and without previous thrombosis.

#### *Suggested next research lines*

Head-to-head comparison among different deep venous reflux approaches, with properly powered study population and long follow-up.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Deep venous reflux can be managed by proper elastic compression and, eventually, by superficial reflux treatment. Deep venous reflux surgical treatment is to be performed only in highly specialized centers and it is still in need of strong scientific validation.

*Suggested pertinent extra readings*

a) Nakayama M. The Incidence, Clinical Importance and Management of Incompetent Gastrocnemius Vein. *Ann Vasc Dis* 2016;9:35-41.

b) Labropoulos N, Tassiopoulos AK, Kang SS Mansour MA, Littooy FN, Baker WH. Prevalence of deep venous reflux in patients with primary superficial vein incompetence. *J Vasc Surg* 2000;32:663-8.

c) Mayberry JC, Moneta GL, DeFrang RD, Porter JM. The influence of elastic compression stockings on deep venous hemodynamics. *J Vasc Surg* 1991;13:91-9.

d) Cornwall JV, Doré CJ, Lewis JD. Graduated compression and its relation to venous refilling time. *Br Med J (Clin Res Ed)* 1987;295:1087-90.

**6. Popliteal vein aneurysm management**

*Query used for the literature search*

(popliteal vein) AND (aneurysm)

*Main findings*

A not univocal definition of popliteal vein aneurysm is present in the literature according to our search. Generally, it is indicated as a persistent isolated vein dilation starting from 1.5 times the normal diameter. Popliteal vein aneurysm is the most common vein dilation of the lower extremity deep venous system and it generally manifests itself by pain, palpable mass, venous hypertension signs and symptoms, thrombo-embolic complications and rupture. Surgery remains the treatment of choice whenever symptomatic. If asymptomatic but saccular, the surgical indication persists because of the thrombo-embolic potential risk. If fusiform, larger than 2 cm aneurysm must be taken into consideration for intervention. Up to our knowledge, no significant large studies confirmed the cut-off diameter for indication to treatment. The most used technical option is tangential aneurismectomy with lateral venorrhaphy. Other possible technical solutions are resection with end-to-end anastomosis or resection with vein/PTFE interposition. No endovascular options have been documented properly up to our search. Ultimately, the technical choice must follow the single case evaluation.<sup>142</sup> A debate remains open in the scientific community regarding the eventual need of inferior vena cava filter temporary insertion in case of ilio-femoral venous thrombosis and if the patient is not fit for surgery or systemic anticoagulation.<sup>143</sup> Globally validated anticoagulation protocols are missing and must be tailored to the single case. Peri-procedural anticoagulation for up to 12 months followed by low

dose aspirin, graduated and intermittent compression use have been proposed, but proper evidence-based validation is needed on the topic.<sup>144</sup> Further data collection is needed before providing high recommendation on this condition management: considering up to 50% of popliteal vein aneurysm have been associated with thrombo-embolic complications, the identification of proper treatment strategy has priority.

*Analyzed literature possible biases*

Not more than 300 cases reported in the literature up to our search.

*Suggested next research lines*

Popliteal vein aneurysm thromboprophylaxis regimen.

*Related statement in layman's term for public vein-lymphatic awareness*

Popliteal vein dilation must be carefully evaluated by a specialist for surgical treatment or lifelong anticoagulation or conservative follow-up.

*Suggested pertinent extra readings*

a) Norimatsu T, Aramoto H. Surgical repair for popliteal venous aneurysm causing severe or recurrent pulmonary thromboembolism: three case reports. *Ann Vasc Dis* 2015;8:56-8.

b) Lutz HJ, Sacuiu RD, Savolainen H. Surgical therapy of an asymptomatic primary popliteal venous aneurysm. *Ann Vasc Surg* 2012;26:729.e7-9.

c) van der Voort EA, De Maeseneer MG. A giant aneurysm of the popliteal vein. *Vasa* 2012;41:229-32.

**7. Venous malformations diagnostic and treatment protocol**

*Query used for the literature search*

((("Vascular Malformations/diagnostic imaging"[Mesh] OR "Vascular Malformations/surgery"[Mesh] OR "Vascular Malformations/therapy"[Mesh] )) AND "Lower Extremity"[Mesh])

*Main findings*

Venous malformation is the most common type of congenital vascular malformation with an incidence of 1 to 2 in 10,000 and a prevalence of 1%. Venous malformations are composed of ectatic venous channels found in the head, neck, limbs, and trunk and are thought to be sporadic in most cases.<sup>145, 146</sup> X-rays can image calcified phleboliths and the degree of dystrophic calcification,

which can be useful in suggesting the presence of venous malformations, as it has been shown that over 1/3 of them have bony changes.<sup>147</sup> Duplex is a useful, non-invasive imaging technique and should be used as the first modality whenever investigating the presence of a vascular malformations, especially for superficial lesions or those in the extremities.<sup>148</sup> Contrast-enhanced magnetic resonance imaging and magnetic resonance angiography are the preferred modalities for pre-procedure diagnosis and interventional planning as well as post-procedure evaluation. Conventional magnetic resonance imaging has 100% sensitivity and 24% to 33% specificity in differentiating vascular from non-vascular malformations.<sup>149</sup> There may be instances when it is prudent to delay intervention in favor of observation, or to avoid intervention if there are no significant symptoms and risks. In such cases, associated complications, such as pain or anemia caused by bleeding, should be treated. Patients with venous malformations in the extremities should be given compression therapy to minimize symptoms like swelling and thrombophlebitis forcing venous blood from the same malformation into the deep venous system.<sup>150</sup> Surgical intervention was traditionally considered to be the initial form of treatment if the lesion could be completely resected and had minimal anatomic and functional consequences. However, sclerotherapy is now the established gold standard.<sup>151</sup>

#### Analyzed literature possible biases

Lack of homogeneity in severity staging.

#### Suggested next research lines

Venous malformation surveillance timeline best protocol identification.

#### Related statement in layman's term for public vein-lymphatic awareness

Venous malformations are often underdiagnosed and require expert evaluation, together with at least ultrasound and, potentially, magnetic resonance assessment.

#### Suggested pertinent extra readings

- a) Markovic JN, Shortell CK. Venous malformations. *J Cardiovasc Surg* 2021;62:456-66.
- b) Hage AN, Treatment of Venous Malformations: The Data, Where We Are, and How It Is Done. *Tech Vasc Interv Radiol* 2018;21:45-54.
- c) Clemens RK, Baumann F, Husmann M, Meier TO, Thalhammer C, MacCallum G, *et al.* Percutaneous sclero-

therapy for spongiform venous malformations - analysis of patient-evaluated outcome and satisfaction. *Vasa* 2017;46:477-83.

### 8. Artero-venous malformations diagnostic and treatment protocol

#### Query used for the literature search

((“Arteriovenous Malformations/diagnostic imaging”[Mesh] OR “Arteriovenous Malformations/drug therapy”[Mesh] OR “Arteriovenous Malformations/radiotherapy”[Mesh] OR “Arteriovenous Malformations/surgery”[Mesh] OR “Arteriovenous Malformations/therapy”[Mesh] )) AND “Lower Extremity”[Mesh]

#### Main findings

AVM represent a rare condition, and they are the least common type of congenital vascular malformations. They can be classified in low-flow, high-flow, and mixed AVMs. High-flow AVMs represent 10% of lower-limb AVMs. The most common place to find them is the cranium, followed by the extremities and finally in the trunk.<sup>152</sup> An early aggressive approach to all AVMs is warranted to reduce, if not prevent, the immediate risk of bleeding as well as the long-term risks of cardiac failure and gangrene. Clinically, it is difficult to select the optimal treatment to enhance long-term success. Surgical excision offers the best opportunity for “cure.” However, diffuse excision of infiltrating AVMs of the extratruncular form can be associated with significant morbidity as well as with failure of attempted cure.<sup>153</sup> Incomplete removal of the AVM is a frequent result of attempts to avoid the high morbidity associated with total excision.<sup>154</sup> Minimally invasive embolization techniques are alternative therapeutic options. The goal of any AVM embolization is to eliminate the AVM nidus. A combination of approaches to deliver embolic agents using transarterial, direct puncture, or retrograde transvenous embolization may be required.<sup>155</sup> The most commonly used embolic agents have been ethanol and n-butyl cyanoacrylate. Additionally, various types of coils, and/or contour particles such as ivalon were used in various combinations, simultaneously or in stages, depending upon the location, severity, and extent of the AVM. Another commonly used agent in AVM treatment is the slowly polymerizing agent Onyx.<sup>156</sup>

#### Analyzed literature possible biases

Heterogenous hemodynamic impact of the artero-venous malformations assessed in the different studies.

*Suggested next research lines*

Artero-venous malformations best imaging options identification.

*Related statement in layman's term for public vein-lymphatic awareness*

An arterial component inside a venous malformation should always be excluded before designing the treatment strategy.

*Suggested pertinent extra readings*

a) Ornelas-Flores MC, Rojas-Reyna GA, Hinojosa-Gutiérrez CG, Leo SG. Endovascular management of a complex high-flow lower limb arteriovenous malformation: Case report and literature review. *Cir Cir* 2021;89(S1):14-9.

b) Maharaj MM, Biju R, Khashram M, Hussain Z. Delayed Fragmentation and Distal Embolization of Retained Microcatheter Causing Lower Limb Ischemia: Case Report and Review of the Literature. *World Neurosurg* 2020;140:369-73.

c) Gao X, Guo J, Tong Z, Guo L, Zhang J, Gu Y. Successful Treatment of Acquired Arteriovenous Fistulas after Iliac Vein Thrombosis. *Ann Vasc Surg* 2020;62:499.e15-.e20.

d) Parin L, Madhu G, Anil T, Sonali B. Anesthetic Management of a Patient with Cowden Syndrome and Review of Anesthetic Concerns. *J Clin Anesth* 2017;38:173-4.

e) Slama R, Long B, Koyfman A. The emergency medicine approach to abdominal vascular graft complications. *Am J Emerg Med* 2016;34:2014-7.

**9. Marginal vein treatment strategies**

*Query used for the literature search*

((“Klippel-Trenaunay-Weber Syndrome/drug therapy” [Mesh] OR “Klippel-Trenaunay-Weber Syndrome/surgery”[Mesh] OR “Klippel-Trenaunay-Weber Syndrome/therapy”[Mesh])) OR (“Umbilical Veins/surgery”[Mesh] OR “Umbilical Veins/therapy”[Mesh])

*Main findings*

A MV is an abnormal superficial draining vein of the lower limb, localized on the lateral aspect of the extremity. This vein is a remnant of primitive embryonic vessels and may exist alone or with anomalies of the deep veins.<sup>157</sup> MV can be detected by ultrasound. During the scan it is important to note the structure of the deep venous system and the hemodynamics within, as this will determine the therapeutic options that would be offered. If the deep veins are not patent or hypoplastic, the MV maybe the only drainage for the

lower limb and hence treating the MV can be detrimental to the limb. Cases of venous gangrene following treatment of MV have been reported in such patients.<sup>158</sup> Treatment of a MV depends on the condition of the deep veins and the extent and symptomatic complaints of the patient. In cases of adults without symptoms, compression stockings are sometimes recommended. MVs are located superficially and involve large perforator veins to the deep veins that make successful treatment of the marginal vein increasingly challenging. Sclerotherapy alone may result in extension of the thrombosis to the deep venous system. Laser therapy may result in skin scar and painful thrombophlebitis in superficial marginal veins. Stripping is risky because of excessive bleeding, hematomas and coexisting vascular anomalies, especially lymphedema. In the past, surgical resection including clear exposure of the veins and ligation of large perforators was recommended.<sup>159</sup> Due to its extremely superficial location beneath the skin, the endovascular obliteration using the laser or radiofrequency is seldom technically applicable. Foam sclerotherapy performed by expert physicians can be a valuable first treatment attempt.<sup>160</sup>

*Analyzed literature possible biases*

Lack of head to head comparison among different techniques for marginal vein treatment.

*Suggested next research lines*

Best technique for marginal vein treatment.

*Related statement in layman's term for public vein-lymphatic awareness*

A pre-operative careful evaluation is mandatory before treatment of veins along the lateral side of the leg since they could represent a venous malformation.

*Suggested pertinent extra readings*

a) Fereydooni A, Nassiri N. Evaluation and management of the lateral marginal vein in Klippel-Trénaunay and other PIK3CA-related overgrowth syndromes. *Journal of vascular surgery Venous and lymphatic disorders* 2020;8:482-93.

b) John PR. Klippel-Trenaunay Syndrome. *Tech Vasc Interv Radiol* 2019;22:100634.

**10. Conservative management for vascular malformations**

*Query used for the literature search*

((“Vascular Malformations/drug therapy”[Mesh] OR “Vascular Malformations/prevention and control”[Mesh])

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OR “Vascular Malformations/radiotherapy”[Mesh] OR “Vascular Malformations/surgery”[Mesh] OR “Vascular Malformations/therapy”[Mesh] )) AND “Lower Extremity”[Mesh]

*Main findings*

The best opportunity for improved quality-of-life for patients with arterio-venous malformations is early diagnosis and management using a combination of conservative, endovascular, and surgical treatments provided by a multidisciplinary team. A multidisciplinary team (specialists from vascular, plastic, otolaryngologic, orthopedic, or pediatric surgery, radiology, dermatology and hematology) is necessary to properly diagnose and coordinate care among disciplines when dealing with these complex cases.<sup>161, 162</sup> Only patients who are symptomatic or have complications of their vascular mal-

formation are considered candidates for therapeutic intervention, given the potential for additional morbidity related to any intervention. Conservative management can be a short- or long-term treatment strategy based on the patient’s symptoms, risks to the limb, and functional imitations and includes extremity compression, medications, physical therapy, and ongoing clinical monitoring. Compression therapy is frequently used as a first-line therapy for low-flow vascular malformations for the alleviation of symptoms. The available evidence suggests that compression therapy may reduce intravascular coagulation, improve symptoms and appearance, diminish oedema, and protect against minor trauma (Figure 4).<sup>163, 164</sup>

*Analyzed literature possible biases*

Lack of homogeneity in the assessed study populations.

*Suggested next research lines*

- Effectiveness of compression therapy in the treatment of congenital vascular malformations.
- Compression dosing and type for venous malformations.

*Related statement in layman’s term for public vein-lymphatic awareness*

Conservative treatment, mainly by compression, is to be taken into consideration for most asymptomatic lower limb venous malformations, together with a follow-up by experts in the specific malformations field.

*Suggested pertinent extra readings*

- Ornelas-Flores MC, Rojas-Reyna GA, Hinojosa-Gutiérrez CG, Leo SG. Endovascular management of a complex high-flow lower limb arteriovenous malformation: Case report and literature review. *Cir Cir* 2021;89(S1):14-9.
- Gao X, Guo J, Tong Z, Guo L, Zhang J, Gu Y. Successful Treatment of Acquired Arteriovenous Fistulas after Iliac Vein Thrombosis. *Ann Vasc Surg* 2020;62:499.e15-.e20.
- Qiu J, Zhou W, Zhou W, Xiong J. Bilateral Persistent Sciatic Artery: Literature Review and Case Report Follow-up for More than Five Years. *Ann Vasc Surg* 2017;41:282.e5-.e10.
- Parin L, Madhu G, Anil T, Sonali B. Anesthetic Management of a Patient with Cowden Syndrome and Review of Anesthetic Concerns. *J Clin Anesth* 2017;38:173-4.



**4. DEEP VENOUS & MALFORMATIONS**

The deep venous system is the main road for the blood to go back to the heart. This section focuses on the pathological change of drainage direction (reflux) and eventual obstruction of the leg deep venous system. A possible cause of obstruction is the formation of a clot (thrombus): an entire separate section is dedicated to the topic.

The below reported statements include also useful information on possible venous dilation (aneurysm) and malformation of the deep venous system. Insights on all these topics are available here: [www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)

**DEEP VENOUS**

- Not only the superficial venous system must be assessed: deep veins of the leg can present a reflux because of spontaneous or post-thrombotic or post-trauma valve damage and/or vein obstruction.
- Patients with superficial venous insufficiency and deep venous reflux might be candidate for superficial venous treatment, yet an expert evaluation of the specific case is needed.
- A narrowing of the iliac vein is present in more than 50% of the population: a caliber reduction alone is not an indication to treatment per se. Only specialized centers should treat iliac vein stenosis and only after careful evaluation of the risk and benefit.
- Ilio-femoral venous stenting for obstruction must be performed after specialist careful evaluation and only in patients affected by severe compression.
- Deep venous reflux can be managed by proper elastic compression and, eventually, by superficial reflux treatment. Deep venous reflux surgical treatment is to be performed only in highly specialized centers and it’s still in need of strong scientific validation.
- Popliteal vein dilation must be carefully evaluated by a specialist for surgical treatment or lifelong anticoagulation or conservative follow up.
- Venous malformations are often underdiagnosed and require expert evaluation, together with at least ultrasound and, potentially, magnetic resonance assessment.
- An arterial component inside a venous malformation should always be excluded before designing the treatment strategy.
- A pre-operative careful evaluation is mandatory before treatment of veins along the lateral side of the leg since they could represent a venous malformation.
- Conservative treatment, mainly by compression, is to be taken into consideration for most asymptomatic lower limb venous malformations, together with a follow up by experts in the specific malformations field.

Figure 4.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding deep venous disease and vascular malformations.

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## 5. Pelvic venous disorders

### 1. Pelvic venous reflux role in pelvic pain pathophysiology

*Query used for the literature search*

(pelvic pain) AND (venous)

#### Main findings

Pelvic venous reflux has been reported as possible cause of pelvic pain in up 30% of women. At the same time, venous reflux can be present in asymptomatic patients manifesting itself with an heterogenous spectrum of signs and symptoms. The relationship between pelvic venous reflux and pain perception is complex in its pathophysiology description and still to be fully understood. Vein dilation *per se* is not enough to lead to both the symptoms and the diagnosis of pelvic venous disorder.<sup>165</sup> Incompetent and dilated ovarian veins can be found in almost 50% of asymptomatic women.<sup>56</sup> Venous hypertension and the related inflammation can be partially compensated by the perineal leaking points, downloading the pressure on the lower limb varicose veins.<sup>166</sup> The hormonal status can influence the symptomatology that usually resolve after menopause: a finding that indirectly could suggest the same hormones role in vein dilation. Indeed, estrogen leads to nitric oxide secretion, resulting in increased dilatation and vein wall deterioration. Data show that estrogen levels can affect nociceptive sensitivity.<sup>167</sup> Another indirect sign of pelvic venous reflux role on pain development can be found in preliminary data showing how a drug able to act on the venous tone demonstrated to decrease pelvic pain and blood pooling.<sup>168</sup> Further investigations are needed to fully understand the intricate pathophysiology connecting pelvic vein reflux and pelvic pain.

#### Analyzed literature possible biases

Lack of objective measurement in pelvic pain measurement.

#### Suggested next research lines

Correlation between pelvic pain and pelvic vein drainage impairment.

#### Related statement in layman's term for public vein-lymphatic awareness

Pain in the lower abdomen and/or back can be caused by a pelvic venous reflux requiring proper expert assessment, including by a vascular specialist.

#### Suggested pertinent extra readings

a) Szaflarski D, Sosner E, French TD, Sayegh S, Lamba R, Katz DS, *et al.* Evaluating the frequency and severity

of ovarian venous congestion on adult computed tomography. *Abdom Radiol* 2019;44:259-63.

b) Mahmoud O, Vikatmaa P, Aho P, Halmesmaki K, Alback A, Rahkola-Soisalo P, *et al.* Efficacy of endovascular treatment for pelvic congestion syndrome. *J Vasc Surg Venous Lymphat Disord* 2016;4:355-70.

c) Borghi C, Dell'Atti L. Pelvic congestion syndrome: the current state of the literature. *Arch Gynecol Obstet* 2016;293:291-301.

d) Phillips D, Deipolyi AR, Hesketh RL, Midia M, Oklu R. Pelvic congestion syndrome: etiology of pain, diagnosis, and clinical management. *J Vasc Interv Radiol* 2014;25:725-33.

### 2. Public awareness in pelvic venous reflux

*Query used for the literature search*

(pelvic congestions syndrome) OR (pelvic venous disorder) AND (awareness)

#### Main findings

Pelvic venous disorders represent a controversial topic in which vascular and gynecology scientific societies still have to properly co-work for best public health awareness orientation. The readability and reliability of the available information for the patient remains suboptimal, hampering appropriate care. A call to action to improve the quantity and quality of online information on the topic and the engagement of the health professionals in reaching out to the public for increasing related health awareness has been recently published.<sup>169</sup> The issue is significant considering around 20% of the gynecologic consultations are due to chronic pelvic pain, and only 40% of them are addressed to the specialist.<sup>170</sup> At the same time, special focus must be used in avoiding under as well as overtreatment of the patients, who must be addressed only to properly trained centers.<sup>171</sup> In UK the incidence of pelvic pain has been reported to be superior to the one of asthma and back pain: improving its management, also by raising awareness on the possible pelvic venous disorder cause, is of paramount importance.<sup>172</sup>

#### Analyzed literature possible biases

Lack of multi-racial public pelvic venous awareness data.

#### Suggested next research lines

Real world data on pelvic venous awareness data.

#### Related statement in layman's term for public vein-lymphatic awareness

Pelvic venous disorder is among the main cause of pelvic pain. Increasing awareness about it among the public is crucial.



*Suggested pertinent extra readings*

a) Aldhafery BF. What family physicians should know about interventional radiology? *J Family Community Med* 2020;27:85-90.

b) Champaneria R, Shah L, Moss J, Gupta JK, Birch J, Middleton LJ, *et al.* The relationship between pelvic vein incompetence and chronic pelvic pain in women: systematic reviews of diagnosis and treatment effectiveness. *Health Technol Assess* 2016;20:1-108.

**3. Pelvic venous disorders symptomatology**

*Query used for the literature search*

(symptoms) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

*Main findings*

Pelvic venous disorder symptomatology has been focused on chronic, dull, unilateral or bilateral pain lasting for at least 6 months. Nevertheless, the symptoms associated with this condition can be extremely variable and frequently absent, therefore making the symptomatology correlation with the hemodynamic impact extremely challenging.<sup>173</sup> Pain can be exacerbated by prolonged standing and by factors increasing abdominal pressure like lifting, constipation and pregnancy. Intercourse can also trigger pelvic venous disorder pain, particularly in younger age according to recent literature.<sup>174</sup> Pain usually worsens during the day and in the first menstruation days and it can present itself in atypical localizations, such as the abdomen, lower back, hips or legs. Other manifestations of pelvic venous disorder may also include headache, dysmenorrhea, rectal discomfort, swollen vulva, vaginal discharge, persistent genital arousal and aspecific gastrointestinal symptoms. A depression of the mood has also been described, together with the role of neurotransmitters related to varicose veins dilation (substance P and neurokinins) that are considered involved in psychological status determination.<sup>165, 175</sup> Pelvic venous disorder symptomatology can clearly affect the quality of life and disease specific tools to assess its objective impact are needed.

*Analyzed literature possible biases*

Heterogeneous assessment methodologies for pelvic pain evaluation.

*Suggested next research lines*

Validation of a disease specific pain score and correlation with the hemodynamic impact of pelvic venous reflux.

*Related statement in layman's term for public vein-lymphatic awareness*

The following symptoms could be associated with a pelvic venous disorder: chronic pelvic pain for more than 6 months, flank pain, pain during sexual intercourse, alterations during the menstrual cycle, difficult/painful urination. Pelvic venous disorder can be also asymptomatic.

*Suggested pertinent extra readings*

a) Barge TF, Uberoi R. Symptomatic pelvic venous insufficiency: a review of the current controversies in pathophysiology, diagnosis, and management. *Clin Radiol* 2022;77:409-17.

b) Leonardi M, Armour M, Gibbons T, Cave A, As-Sanie S, Condous G, *et al.* Surgical interventions for the management of chronic pelvic pain in women. *Cochrane Database Syst Rev* 2021 Dec 20;12(12):CD008212.

c) Ganeshan A, Upponi S, Hon LQ, Uthappa MC, Warakaulle DR, Uberoi R. Chronic pelvic pain due to pelvic congestion syndrome: the role of diagnostic and interventional radiology. *Cardiovasc Intervent Radiol* 2007;30:1105-11.

**4. Pelvic venous disorders signs**

*Query used for the literature search*

(symptoms) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

*Main findings*

As per the symptomatology, pelvic venous disorders signs are extremely variable in their presentation. Due to the many abdominal, pelvic and lower limb anatomical connections, pelvic vein dilation/reflux/inflammation can lead to signs manifesting themselves in different regions, such as vulval swelling, vaginal discharge, abnormal vaginal bleeding, perineal and/or lower limb varices and/or edema, hemorrhoids, hematuria.<sup>165</sup> Vulvar varices prevalence in pelvic venous disorders patients has been reported in up to 40% of cases.<sup>176</sup> A detailed investigation of the possible pelvic leaking points must always be included in a lower limb scanning for chronic venous disease in order to avoid undertreatment of main reflux sources. Recent literature also postulated the possible pelvic venous disorder role in venous leg ulceration as well as in infertility.<sup>177, 178</sup> A careful clinical assessment of the patient, including not only the pelvic region, is mandatory for an appropriate diagnostic work up of the pelvic venous disorder condition.

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*Analyzed literature possible biases*

Heterogeneous study populations with potential comorbidities leading to aspecific signs.

*Suggested next research lines*

Investigation of eventual correlation between pelvic reflux/stasis severity and clinical signs development.

*Related statement in layman's term for public vein-lymphatic awareness*

Pelvic venous disorder can manifest itself by dilated veins in the genital and/or lower limb region, as well as by vaginal swelling and/or discharge, menstrual cycle alteration, blood in the urine, hemorrhoids.

*Suggested pertinent extra readings*

a) Barge TF, Uberoi R. Symptomatic pelvic venous insufficiency: a review of th current controversies in pathophysiology, diagnosis, and management. Clin Radiol 2022;77:409-17.

b) Khilnani NM, Winokur RS, Scherer KL, Meissner MH. Clinical Presentation and Evaluation of Pelvic Venous Disorders in Women. Tech Vasc Interv Radiol 2021;24:100730.

c) Szymanski J, Jakiel G, Slabuszewska-Jozwiak A. Pelvic venous insufficiency - an often-forgotten cause of chronic pelvic pain. Ginekol Pol 2020;91:704-8.

d) Mathur M, Scoult LM. Nongynecologic Causes of Pelvic Pain: Ultrasound First. Obstet Gynecol Clin North Am 2019;46:733-53.

e) Almeida GR, Silvinato A, Simões R, Buzzini RF, Bernardo WM. Pelvic congestion syndrome - treatment with pelvic varicose veins embolization. Rev Assoc Med Bras (1992) 2019;65:518-23.

**5. Pelvic venous disorders risk factors**

*Query used for the literature search*

(risk factors) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

*Main findings*

Pelvic venous disorder risk factors reported in the literature include more than three pregnancies, pelvic venous anatomy alteration, history of pelvic pain, increased oestrogens levels, polycystic ovary syndrome, prolapsed uterus, previous pelvic surgery, prolonged standing and conditions increasing abdominal pressure such as lifting.<sup>179</sup> Lower limb chronic venous insufficiency is not rarely associated with pelvic venous disorder, yet, up to the authors knowledge,

no significant literature has identified an eventually related statistically significant risk factor role.<sup>180</sup> Differently from the leg district, preliminary data suggest a lower BMI can represent a risk factor for pelvic venous disorder.<sup>181</sup> The identification of family history of pelvic pain as risk factor suggests a genetic and/or ethnic predisposition could be present, yet more solid evidence-based data are needed on the topic. Mutations of FOXC2, TIE2, NOTCH3, type 2 transforming growth factor-β and thrombomodulin genes have been considered potentially involved in pelvic reflux development.<sup>179</sup>

*Analyzed literature possible biases*

Lack of large homogeneous data collections allowing a confirmation of the possible risk factors.

*Suggested next research lines*

Multi-center studies investigating possible risk factors excluding possible confounding comorbidities.

*Related statement in layman's term for public vein-lymphatic awareness*

More than three pregnancies, prolonged standing and abdominal efforts can increase the risk of pelvic venous disorders. A genetic predisposition might be involved but more research is needed on the topic.

*Suggested pertinent extra readings*

a) Kim AS, Greyling LA, Davis LS. Vulvar Varicosities: A Review. Dermatol Surg 2017;43:351-6.

b) Champaneria R, Shah L, Moss J, Gupta JK, Birch J, Middleton LJ, *et al.* The relationship between pelvic vein incompetence and chronic pelvic pain in women: systematic reviews of diagnosis and treatment effectiveness. Health Technol Assess 2016;20:1-108.

c) Mahmoud O, Vikatmaa P, Aho P, Halmesmäki K, Al-bäck A, Rahkola-Soisalo P, *et al.* Efficacy of endovascular treatment for pelvic congestion syndrome. J Vasc Surg Venous Lymphat Disord 2016;4:355-70.

**6. Pelvic venous disorders diagnostic protocol**

*Query used for the literature search*

(diagnosis) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

*Main findings*

A univocal diagnosis of pelvic venous disorder is challenging due to the blurred clinical scenario and the still to be properly investigated correlation with the instru-

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mental diagnostics findings. While the detection of the pelvic reflux and/or vein dilation is easily obtainable, its direct correlation with the signs and symptoms can be uncertain. The differential diagnosis must include gastroenterology, obgyn, musculoskeletal, neurological, psychological and urological conditions. An attempt to systematize the clinical scenario and the related diagnostic work up has been recently made by the Symptoms-Varices-Pathophysiology classification.<sup>173</sup> After a careful history and clinical evaluation, ultrasound remains the first fundamental diagnostic approach to the patient. This must include a transabdominal assessment in various body positions, including reverse-Trendelenburg to facilitate reflux evocation. Transvaginal and transperineal scanning should be included in the case evaluation, favoring also the eventual detection of other possible gynaecological causes and of lower limb venous drainage involvement, respectively.<sup>182</sup> Vein dilation detection has been considered a positive predicting factor in the past, yet, almost 50% of asymptomatic patients can present significantly enlarged vessels.<sup>56</sup> Computed tomography and magnetic resonance assessment are of paramount importance to better define the pelvic drainage compromise, yet they remain based on mainly caliber parameters whose cut off values still lack proper validation.<sup>183</sup> While diagnostic laparoscopic is still largely used, it should be remembered that up to 90% of pelvic venous disorders can be missed by this approach.<sup>180</sup> Venography remains the gold standard for final pelvic venous disorder diagnosis. Since it is an invasive procedure, it should be reserved after properly planned diagnostic work up as per the above description and in case of interventional therapy intent.<sup>184</sup>

#### Analyzed literature possible biases

Lack of head-to-head comparison among different diagnostic protocols.

#### Suggested next research lines

- Head-to-head comparison among different diagnostic protocols.
- Protocols for pelvic venous thrombosis identification.

#### Related statement in layman's term for public vein-lymphatic awareness

Pelvic venous disorder diagnosis requires a detailed history and clinical evaluation, followed by expert ultrasound scanning of the abdominal and pelvic region, together with the lower limbs. Magnetic resonance and/or computed tomography might be helpful. Venography is an invasive

test and must be performed only after proper risk/benefit evaluation.

#### Suggested pertinent extra readings

a) Roditi G, Wieben O, Prince MR, Hecht EM. MR Angiography Series: Abdominal and Pelvic MR Angiography. *Radiographics* 2022;42:E94-E95.

b) Barge TF, Uberoi R. Symptomatic pelvic venous insufficiency: a review of the current controversies in pathophysiology, diagnosis, and management. *Clin Radiol* 2022;77:409-17.

c) Kolber MK, Cui Z, Chen CK, *et al.* Nutcracker syndrome: diagnosis and therapy. *Cardiovasc Diagn Ther* 2021;11:1140-9.

d) Arnaoutoglou C, Variawa RS, Zarogoulidis P, *et al.* Advances of Laparoscopy for the Diagnosis of Pelvic Congestion Syndrome. *Medicina (Kaunas)* 2021;57:1041.

### 7. Pelvic venous disorders indication to treatment

#### Query used for the literature search

(treatment) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

#### Main findings

Pelvic venous disorder indication to treatment requires an accurate evaluation of each single specific case, in order to avoid under or overtreatment. Conservative measures have been reported in the form of proper life habits, venous active drugs (micronized purified flavonoid fraction) and graduated compression. Yet, long term data are missing, therefore making this topic worthy to be further investigated. No stable significant results have been reported by hormonal therapy. Surgical approaches for pelvic vein ablation demonstrated to be not competitive against endovascular strategies, yet specific treatment protocols have not been validated at a global level up to the knowledge of the authors. Indeed, technical and strategical notes on the procedure varies quite significantly in the literature, not demonstrating a clear advantage of one over the other, including for the comparison among embolic agents such as sclerosants, coils and plugs.<sup>185</sup> Also the post-procedural clinical improvement has been reported heterogeneously, ranging from 47% to 100% of cases.<sup>186</sup> Preliminary data suggest successful treatment can decrease infertility, nevertheless very few cases have been investigated and more research is needed.<sup>178</sup> In case of hemodynamically and clinically significant iliac vein stenosis coexistence, removal of the obstruction is suggested together with embolization of the refluxing pelvic veins, otherwise the risk

of clinical unsuccess is higher than 80%.<sup>187</sup> Left renal vein stenting in the context of nutcracker syndrome and pelvic venous disorders has demonstrated some preliminary benefit, but the published data are sparse and weak: considering the procedural risk, an extremely careful evaluation should be performed before giving this indication.<sup>188</sup>

*Analyzed literature possible biases*

Lack of objective outcome measures.

*Suggested next research lines*

Head-to-head comparison among the different treatment protocols.

*Related statement in layman's term for public vein-lymphatic awareness*

Indication to treatment must be preceded by a venography performed in a high expertise medical center and can not be based just on venous dilation finding.

*Suggested pertinent extra readings*

a) Barge TF, Uberoi R. Symptomatic pelvic venous insufficiency: a review of the current controversies in pathophysiology, diagnosis, and management. *Clin Radiol* 2022;77:409-17.

b) Cosin Sales O. Ultrasound-guided interventional radiology procedures on veins. *Radiologia (Engl Ed)* 2022;64:89-99.

c) Bałabuszek K, Toborek M, Pietura R. Comprehensive overview of the venous disorder known as pelvic congestion syndrome. *Ann Med* 2022;54:22-36.

d) Leonardi M, Armour M, Gibbons T, *et al.* Surgical interventions for the management of chronic pelvic pain in women. *Cochrane Database Syst Rev* 2021 Dec 20;12:CD008212.

**8. Pelvic venous disorders treatment procedural complications management**

*Query used for the literature search*

(treatment complications) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

*Main findings*

Pelvic venous disorders conservative management performed by compression and venous active drugs is generally safe and includes the mild complications already reported in this document chapter dedicated to graduated stockings and pharmacology use. Hormonal therapy addressed to induce a hypoestrogenic state is generally safe and it includes

the possible complications associated with the use of gonadotropin-releasing hormone agonists combined oral contraceptives, progestins: among these, weight gain and fluid retention could work against the venous drainage improvement.<sup>189</sup> Ligation of incompetent ovarian veins and bilateral salpingo-oophorectomy and hysterectomy are clearly invasive procedures whose complications can become significant, among which in particular bleeding, infection, ureter/bladder damage, ovary failure.<sup>190</sup> Mini-invasive endovascular procedures are to be preferred whenever an intervention is indicated. Among the major complications reported following these procedures there are coils migration and protrusion. In such case, both retrieval by snare technique and conservative approaches were documented. Minor complications are related to the traditional venography approach (access site hematoma, contrast extravasation).<sup>191</sup> Up to 20% of cases present a post-embolization syndrome characterized by pelvic pain, hyperthermia and tenderness around the embolized vein. Up to our knowledge, no mortality or major incident was reported, nevertheless maximum care must be paid in these procedures performance and only specialized centers should manage these procedures.<sup>165</sup>

*Analyzed literature possible biases*

Lack of real-world data.

*Suggested next research lines*

International registry on pelvic venous disorder treatment complications.

*Related statement in layman's term for public vein-lymphatic awareness*

Embolization of pelvic veins by coils and sclerotherapy is a safe, but severe complications can happen. Only expert Centers must perform these procedures.

*Suggested pertinent extra readings*

a) Joh M, Grewal S, Gupta R. Ovarian Vein Embolization: How and When Should It Be Done? *Tech Vasc Interv Radiol* 2021;24:100732.

b) Tiralongo F, Distefano G, Palermo M, *et al.* Liquid and Solid Embolic Agents in Gonadal Veins. *J Clin Med* 2021;10:1596.

c) Bendek B, Afuape N, Banks E, Desai NA. Comprehensive review of pelvic congestion syndrome: causes, symptoms, treatment options. *Curr Opin Obstet Gynecol* 2020;32:237-42.

d) Taskin O, Sahin L, Gavrillov SG, Lazarashvili Z. Medical treatment of pelvic congestion syndrome. *Phlebology* 2016;23:146-51.

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## 9. Renal vein compression management

### *Query used for the literature search*

(nutcracker syndrome)

### *Main findings*

Nutcracker Syndrome is a condition arising from an aortomesenteric angle compressing the left renal vein or, more rarely, from a retroaortic left renal vein compressed against the vertebral column. Circumaortic or duplicated left renal vein have also been reported in simultaneously anterior and posterior compression syndromes. Other causes of left renal vein compression have been identified in association with lymphadenopathy or malignancy, pregnancy, lordosis, weight loss and intestinal malrotation. Its diagnosis includes a variety of heterogeneous signs and symptoms, therefore the exact prevalence remains undetermined. Typical manifestation includes hematuria, proteinuria and flank or pelvic pain.<sup>192</sup> Ultrasound scanning followed by computed tomography and/or magnetic resonance imaging can provide useful findings, while catheter venography and pressure measurement are usually necessary for the diagnosis. Univocal ultrasound criteria are still missing. In the same way, left renal vein caliber and aorto-mesenteric angle values variations have been reported in the literature, yet with a sensitivity and specificity never superior to 91% up to our knowledge. IVUS can be of value in the completion of the diagnosis, as well as a cystoscopy assessing the eventual hematuria.<sup>193</sup> Conservative approach, eventually by angiotensin converting enzyme inhibitors in case of orthostatic proteinuria, should be first taken into consideration in pediatric nutcracker syndrome patients in whom the growth is usually associated with a spontaneous resolution.<sup>194</sup> Renal vein transposition remains the gold standard treatment for symptomatic patients. Laparoscopic or robot-assisted procedures have been reported, yet the percentage of re-stenosis has been reported to be over 65%. In case of need, auto-transplantation remains a valid option, despite the technically associated more possible complications. Stent placement has also been proposed in small series. Migration has been already reported in 6.7% cases, confirming the need of relying always only on specialized centers and of producing more data on the topic.<sup>195</sup>

### *Analyzed literature possible biases*

Lack of correlation between clinical and hemodynamic findings with possible heterogeneous study populations.

### *Suggested next research lines*

Long term head-to-head comparison among the different treatment options.

### *Related statement in layman's term for public vein-lymphatic awareness*

Left flank or pelvic pain and blood in the urine can be caused by an anatomical compression of the left renal vein (Nutcracker Syndrome): the management of the condition require a highly specialized center.

### *Suggested pertinent extra readings*

a) Miró I, Serrano A, Pérez-Ardavín J, March JA, Polo A, Conca MÁ, *et al.* Eighteen years of experience with pediatric nutcracker syndrome: the importance of the conservative approach. *J Pediatr Urol* 2020;16:218.e1-6.

b) Wu Z, Zheng X, He Y, Fang X, Li D, Tian L, *et al.* Stent migration after endovascular stenting in patients with nutcracker syndrome. *J Vasc Surg Venous Lymphat Disord* 2016;4:193-9.

c) Hannick JH, Blais AS, Kim JK, Traubici J, Shiff M, Book R, *et al.* Prevalence, Doppler ultrasound findings, and clinical implications of the nutcracker phenomenon in pediatric varicoceles. *Urology* 2019;128:78-83.

## 10. Pelvic venous disorders follow-up

### *Query used for the literature search*

(follow up) AND ((pelvic venous disorder) OR (pelvic congestion syndrome))

### *Main findings*

Pelvic venous disorder recurrence incidence is biased by the lack of objective outcome measures and standardized treatment protocols.<sup>165</sup> A recent clinic case report pointed out the possible pelvic venous disorder recurrence in anatomical districts not previously treated, such as the median sacral vein, pointing out how, as per the lower limb, reflux reappearance can involve previously treated vessels as well as connected networks.<sup>166</sup> Up to our search, validated follow-up protocols following pelvic venous disorders treatment are missing. Post-procedural symptoms resolution might require months.<sup>197</sup> Proper clinical and ultrasound re-assessment timing should be identified, taking into consideration the single cases specifics (Figure 5).

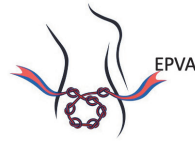
### *Analyzed literature possible biases*

Lack of objective outcomes allowing validation of specific follow-up protocols.

## 5. PELVIC VENOUS DISORDERS

Like for the varicocele in the male gender, the female can be affected by venous reflux in the pelvic region. The phenomenon can be asymptomatic or associated with a significant symptomatology.

The condition is extremely frequent, yet too often underdiagnosed and/or managed inadequately. Awareness of this condition is mandatory for both health professionals and public. Detailed information based on scientific data are available here: [www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)



### PELVIC VENOUS DISORDERS

1. Pain in the lower abdomen and/or back can be caused by a pelvic venous reflux requiring proper expert assessment, including by a vascular specialist.
2. Pelvic venous disorder is among the main cause of pelvic pain. Increasing awareness about it among the public is crucial.
3. The following symptoms could be associated with a pelvic venous disorder: chronic pelvic pain for more than 6 months, flank pain, pain during sexual intercourse, alterations during the menstrual cycle, difficult/painful urination. Pelvic venous disorder can be also asymptomatic.
4. Pelvic venous disorder can manifest itself by dilated veins in the genital and/or lower limb region, as well as by vaginal swelling and/or discharge, menstrual cycle alteration, blood in the urine, hemorrhoids.
5. More than 3 pregnancies, prolonged standing and abdominal efforts can increase the risk of pelvic venous disorders. A genetic predisposition might be involved but more research is needed on the topic.
6. Pelvic venous disorder diagnosis requires a detailed history and clinical evaluation, followed by expert ultrasound scanning of the abdominal and pelvic region, together with the lower limbs. Magnetic Resonance and/or Computed Tomography might be helpful. Venography is an invasive test and must be performed only after proper risk/benefit evaluation.
7. Indication to treatment must be preceded by a venography performed in a high expertise medical center and can not be based just on venous dilation finding.
8. Embolization of pelvic veins by coils and sclerotherapy is a safe but severe complications can happen. Only expert Centers must perform these procedures.
9. Left flank or pelvic pain and blood in the urine can be caused by an anatomical compression of the left renal vein (Nutcracker syndrome): the management of the condition require a highly specialized center.
10. Pelvic symptoms improvement can require some months after the treatment. A specialist must reassess along time the condition.

Figure 5.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding pelvic venous disorders.

### Suggested next research lines

Mid- and long-term post procedural follow-up aimed to identify the best timing for patient re-assessment.

### Related statement in layman’s term for public vein-lymphatic awareness

Pelvic symptoms improvement can require some months after the treatment. A specialist must reassess along time the condition.

### Suggested pertinent extra readings

a) Maratto S, Khilnani NM, Winokur RS. Clinical Presentation, Patient Assessment, Anatomy, Pathophysiology, and Imaging of Pelvic Venous Disease. *Semin Intervent Radiol* 2021;38:233-8.

b) Senechal Q, Echegut P, Bravetti M, Florin M, Jarbouli L, Bouaboua M, *et al.* Endovascular Treatment of Pelvic

Congestion Syndrome: Visual Analog Scale Follow-Up. *Front Cardiovasc Med* 2021 Nov 17;8:751178.

## 6. Venous thrombosis

### 1. Proper venous thrombotic risk assessment

#### Query used for the literature search

((("venous thrombosis" OR "venous thromboembolism" OR "VTE") AND ("risk assessment model") AND ("meta-analysis" OR "review"))

#### Main findings

Venous thromboembolism events cause substantial morbidity, mortality, and long-term sequelae, but can be prevented with the judicious use of mechanical and pharmacological prophylaxis. For patient groups with elevated baseline thrombo-embolic risk, including surgery patients, hospitalized patients, and patients with cancer, clinicians should perform individualized risk assessments using models that have been validated within the patient population of interest.<sup>198</sup> Individualized risk assessment is key to targeting patient groups most likely to benefit from pharmacological prophylaxis while minimizing the risk of bleeding side effects. Patient risk scores should be used as clinical decision tools to determine appropriate evidence-based levels of VTE prophylaxis.<sup>199</sup> There are many known risk factors for venous thrombo-embolism, including age, obesity, immobility, personal and family history (including second and third-degree relatives), inherited disorders of coagulation, cancer, trauma, sepsis, and surgical operations, and this list continues to grow as further risk factors are discovered. The more risk factors that a patient has, the higher their overall risk and the greater the need for pharmacological prophylaxis. High quality evidence supports the use of 7-10 days of prophylaxis for patients at high risk, and 30 days of prophylaxis for patients determined to be at very high risk.<sup>200</sup> The Caprini, Geneva, IMPROVE, Kucher, and Padua risk assessment models have been externally validated for the prediction of venous thrombo-embolism in various medical populations, while the Khorana score is commonly used in patients with cancer.<sup>199, 201</sup> The Caprini Risk Score has been validated in well over 100 publications among multiple surgical and medical populations. The score has several advantages over other risk scores. The score is more comprehensive and specifically queries family history, which has been proven to be a major risk factor. The high sensitivity and negative predictive value of the Caprini makes it the ideal tool to determine which patients are at low risk

and can safely avoid thromboprophylaxis during a hospitalization or after surgery. It has also been implemented as part of hospital prophylaxis protocols that successfully reduced rates of venous thromboembolism.<sup>200</sup>

#### *Analyzed literature possible biases*

Heterogeneous clinical vs. lab thrombosis detection outcome measure in the different studies.

#### *Suggested next research lines*

- Risk assessment in non-hospitalized patients without cancer.
- Risk assessment in outpatients undergoing minor procedures.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Venous thromboembolism is a blood clot of the veins of the legs (deep venous thrombosis), or lungs (pulmonary embolism). Patients should be informed about their risk factors.

#### *Suggested pertinent extra readings*

a) Autar R. Evidence for the prevention of venous thromboembolism. *British journal of nursing* 2006;15:980-6.

b) Barbar S, Prandoni P. Scoring systems for estimating risk of venous thromboembolism in hospitalized medical patients. *In Seminars in thrombosis and hemostasis* 2017;43:460-8.

c) Cohen AT, Alikhan R, Arcelus JI, Bergmann JF, Haas S, Merli GJ, Spyropoulos AC, Tapson VF, Turpie AG. Assessment of venous thromboembolism risk and the benefits of thromboprophylaxis in medical patients. *Thrombosis and Haemostasis* 2005;94:750-9.

d) Cronin M, Dengler N, Krauss ES, Segal A, Wei N, Daly M, *et al.* Completion of the updated Caprini risk assessment model (2013 version). *Clinical and Applied Thrombosis/Hemostasis* 2019;25:1076029619838052.

## **2. Venous thrombosis diagnostic work-up**

#### *Query used for the literature search*

((“venous thrombosis” OR “venous thromboembolism” OR “VTE”) AND (“diagnosis” OR “workup”) AND (“meta-analysis” OR “systematic review”))

#### *Main findings*

For patients with clinically suspected VTE but with no past or family history of VTE, the rate of thrombo-embolism diagnosis is just 20%. Therefore, diagnostic work-up must balance

the importance of ruling out this highly morbid condition and minimize excessive diagnostic investigations for low-risk patients. The symptoms with the highest predictive value for lower extremity deep venous thrombosis are swelling, cramping, or discomfort in the thigh or calf. Other common symptoms include warmth (calor), erythema (rubor), a palpable cord, and visibly bulging leg veins.<sup>202</sup> Symptoms for pulmonary embolism are less specific, but include tachypnea, tachycardia, shortness of breath, chest pain, and hemoptysis.<sup>203</sup> Clinicians should rely on validated clinical decision tools, such as the Wells (thrombosis and embolism) and Geneva (embolism) Scores, that evaluate patient symptoms and physical examination findings to determine pre-test probability. In patients with low pre-test probability of venous thrombo-embolism, age-adjusted D-dimer is a highly sensitive test to rule out a diagnosis, but it lacks specificity to confirm diagnosis.<sup>204</sup> The exceptions to this rule are hospitalized patients and patients with a history of thrombosis or embolism, in whom the Wells and Geneva scores have not been validated for predicting venous thrombo-embolism. Therefore, these patients should undergo duplex imaging to rule out deep venous thrombosis when suspected.<sup>205</sup> In patients with intermediate-to-high pre-test probability of deep venous thrombosis or elevated D-dimer, compression ultrasonography of the extremity is the preferred diagnostic test, as it is both sensitive and highly specific. However, venography remains the gold standard for deep venous thrombosis diagnosis and is much more accurate in patients without deep venous thrombosis symptoms. For patients with intermediate-to-high pre-test probability of pulmonary embolism or elevated D-dimer, computed tomography pulmonary angiography and ventilation-perfusion scans are the diagnostic approaches of choice. In cancer patients with suspected deep venous thrombosis, compression ultrasonography is the first-line diagnostic modality.<sup>202</sup>

#### *Analyzed literature possible biases*

Many risk scores specifically exclude patients with a personal history of venous thromboembolism from consideration.

#### *Suggested next research lines*

Future research should consider the most sensitive tools to rule out recurrent venous thrombo-embolism among hospitalized patients and patients with prior events.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Symptoms of a deep venous thrombosis in the arms or legs include pain, swelling, redness, tenderness, fever, bulging veins, and skin discoloration. Symptoms of a pulmonary

embolism include chest pain, fast heart rate, coughing up blood, and shortness of breath.

*Suggested pertinent extra readings*

a) Di Minno MN, Calcaterra I, Papa A, Lupoli R, Di Minno A, Maniscalco M, *et al.* Diagnostic accuracy of D-Dimer testing for recurrent venous thromboembolism: A systematic review with meta-analysis.: VTE recurrence and D-dimer. *Eur J Intern Med* 2021;89:39-47.

b) Wang Q, Yuan L, Ding X, Zhou Z. Prediction and Diagnosis of Venous Thromboembolism Using Artificial Intelligence Approaches: A Systematic Review and Meta-Analysis. *Clin Appl Thromb Hemost* 2021;27:10760296211021162.

c) Stals MA, Takada T, Kraaijpoel N, van Es N, Büller HR, Courtney DM, *et al.* Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Clinically Relevant Patient Subgroups. *Ann Intern Med* 2022;175:244-55.

d) Silveira PC, Ip IK, Goldhaber SZ, Piazza G, Benson CB, Khorasani R. Performance of Wells score for deep vein thrombosis in the inpatient setting. *JAMA Intern Med* 2015;175:1112-7.

**3. Thrombotic risk management in obese and chronic venous disease patients**

*Query used for the literature search*

((“venous thrombosis” OR “venous thromboembolism” OR “VTE”) AND (“obesity” OR “varicose” OR “chronic venous disease” OR “CVD”) AND (“risk”) AND (“meta analysis” OR “Systematic Review”))

*Main findings*

Patients with obesity (defined as a BMI of  $\geq 30$  kg/m<sup>2</sup>) are at significantly higher risk of venous thrombo-embolism compared to patients at a normal weight, and this risk increases linearly with increased BMI.<sup>206</sup> Women may also be at risk at a BMI of  $\geq 25$  kg/m<sup>2</sup>, and are at much higher risk if they are taking oral contraceptive pills.<sup>200</sup> Physiologic changes in obese patients, including impaired venous return, the inflammatory effects of adipose tissue, and vessel wall alterations, have all been shown to influence the formation of deep venous thrombosis.<sup>207</sup> Obesity can also be associated with obstructive sleep apnea, another independent risk factor for venous thrombo-embolism. Obesity is also a risk factor for venous thrombo-embolism recurrence. Somewhat surprisingly, obesity does appear to be protective against mortality in patients who do suffer a pulmonary embolism, although this relationship has not been fully explained.<sup>200</sup> Patients with chronic venous disease, including

varicose veins, spider telangiectasias, and reticular veins, have up to 7 times the risk of venous thromboembolism. The associated valvular incompetence, venous hypertension, inflammatory changes, and vein wall alterations influence venous thrombo-embolism formation *via* all three factors of Virchow’s triad.<sup>200</sup> For hospitalized patients with obesity or venous insufficiency, individualized risk assessment should guide risk stratification and prophylaxis approaches. Research has focused on identifying optimal prophylaxis strategies in obese patients; however, no clearly superior approaches have yet been identified in this patient group. Weight-based dosing of prophylactic unfractionated heparin does not appear to increase bleeding risk in obese patients and is associated with increases in factor Xa levels, but has not been shown to decrease VTE events.<sup>208</sup>

*Analyzed literature possible biases*

Because there is no consensus approach for “weight-based” dosing among obese patients, there is significant heterogeneity between studies comparing weight-based to standard prophylactic dosing.

*Suggested next research lines*

Optimal prophylaxis strategies in patients with obesity.

*Related statement in layman’s term for public vein-lymphatic awareness*

Patients who are obese or who have varicose veins are at increased risk of blood clots.

*Suggested pertinent extra readings*

a) Giorgi-Pierfranceschi M, López-Núñez JJ, Monreal M, *et al.* Morbid obesity and mortality in patients with VTE: findings from real-life clinical practice. *Chest* 2020 Jun 1;157(6):1617-25.

b) Chang SL, Huang YL, Lee MC, Hu S, Hsiao YC, Chang SW, *et al.* Association of varicose veins with incident venous thromboembolism and peripheral artery disease. *JAMA* 2018;319:807-17.

c) Cushman M, O’Meara ES, Heckbert SR, *et al.* Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology. *Thrombosis Res* 2016 Aug 1;144:127-32.

**4. Proper use of genetic testing for venous thromboembolism**

*Query used for the literature search*

((“venous thrombosis” OR “venous thromboembolism” OR “VTE”) AND (“genetic” OR “inherited thrombo-

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philia”) AND (“testing” OR “diagnosis” OR “risk”) AND (“meta analysis” OR “Systematic Review”)

### Main findings

There are many inherited genetic risk factors for VTE, including non-O blood type (the most common inherited risk factor for VTE), protein C and S deficiency, factor V Leiden, antithrombin deficiency, prothrombin G20210A, and methylentetrahydrofolate reductase (MTHFR). These inherited risk factors increase VTE risk at any age, but commonly present with VTE in patients younger than 40 years old.<sup>209</sup> Screening for inherited thrombophilia is controversial, and may only be performed for specific at-risk groups when it is likely to change management. There is no replacement for a thorough personal and family history and physical exam to evaluate patient risk and determine the need for screening. Current expert recommendations include genetic testing after unprovoked VTE in patients younger than 50, VTE in pregnant patients/hormone therapy, and VTE in patients with a positive FH. In these patient groups, patients who test positive can be counseled about preventing VTE recurrence by avoiding further risk factors such as oral contraceptives or smoking and using prophylaxis in high-risk events such as surgery.<sup>43, 210</sup> Screening may also be performed in patients with a history of multiple pregnancy loss due to the strong association with inherited thrombophilias, and in patients with thrombosis in unusual locations (e.g. cerebral venous sinus thrombosis, porto-mesenteric venous thrombosis).<sup>211</sup> Genetic testing should be considered for young women with a positive family history of VTE prior to oral contraceptive use.<sup>209, 210</sup>

Physicians should be aware that direct oral anticoagulants (DOAC) use can affect functional assays like deficiency of natural anticoagulants. DOACs typically need to be held for 4-5 half lives to prevent interference with thrombophilia assays. Although data are limited, DOACs appear to be safe and effective in treating VTE for patients with inherited thrombophilias.<sup>43</sup>

### Analyzed literature possible biases

There is an inherent publication bias favoring studies that find a significant association between specific genes or variants and VTE. The use of meta-analyses to determine the most significant inherited risk factors mitigates, but does not eliminate, this bias.

### Suggested next research lines

Inherited factors weakly associated with recurrent VTE. Because most guidelines recommend testing for inherited

thrombophilia after unprovoked VTE, it would be important to know which thrombophilias are most associated with recurrence. There is a need for further evidence to support the use of DOACs in the management of thrombophilias.

### Related statement in layman's term for public vein-lymphatic awareness

Genetic testing may be suggested in a first episode of unprovoked thrombosis for patients under 50 years old, thrombosis with the only risk factor of hormonal therapy or pregnancy, and recurrent VTE if it will affect the further clinical decision on treatment and prophylaxis.

### Suggested pertinent extra readings

a) Zhang Y, Zhang Z, Shu S, Niu W, Xie W, Wan J, *et al.* The genetics of venous thromboembolism: a systematic review of thrombophilia families. *J Thromb Thrombolysis* 2021;51:359-69.

b) Lindström S, Brody JA, Turman C, Germain M, Bartz TM, Smith EN, *et al.* A large-scale exome array analysis of venous thromboembolism. *Genet Epidemiol* 2019;43:449-57.

c) Lindström S, Wang L, Smith EN, *et al.* Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood* 2019;134:1645-57.

d) De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. *Thrombosis Haemost* 2013;110:697-705.

## 5. Cancer related venous thrombosis management

### Query used for the literature search

(“venous thrombosis” OR “venous thromboembolism” OR “VTE”) AND (“cancer” OR “malignancy”) AND (“management” OR “treatment”) AND (“meta-analysis” OR “systematic Review”)

### Main findings

Patients with cancer are at high risk of developing VTE as well as a higher risk of VTE recurrence and should be evaluated with validated risk assessment tools to determine the need for prophylaxis. In particular, VTE risk is much higher in patients with pancreatic, stomach, brain, lung, and ovarian cancer. Chemotherapy and hormonal therapy also independently increase VTE risk. Hospitalized patients with cancer should still undergo individualized risk screening with validated tools such as the Caprini

and Padua assessments to determine the utility of thromboprophylaxis.<sup>212</sup>

For patients that develop VTE, current guidelines recommend initial management with low molecular weight heparin (LMWH), although recently published guidelines also endorse the use of DOACs.<sup>213</sup> Both DOACs and LMWH are recommended for short-term (3-6 months) and long-term (over 6 months) VTE management. The most recent update to the CHEST guidelines favors DOACs over LMWH for acute VTE in cancer patients for both initiation and treatment phases.<sup>214</sup> Randomized clinical trial data in cancer patients show that DOACs have lower rates of recurrent VTE than LMWH, but may have a slightly higher rate of clinically significant bleeding events. In particular, edoxaban and rivaroxaban may increase the risk of gastrointestinal bleed in luminal malignancies. Evidence clearly favors the use of oral anticoagulants or LMWH over warfarin for VTE treatment in cancer patients.<sup>213</sup> See section 6.9 for further detail on the use of DOACs. One area of controversy is screening for occult cancer in patients with unprovoked VTE, an association first noted by Trousseau in the 1860s. A number of studies have found that aggressive screening strategies were not associated with improved outcomes in patients with unprovoked VTE. Based on subgroup analyses, however, it has been suggested that aggressive screening with abdomino-pelvic ultrasound or PET/CT may benefit patients with unprovoked VTE and three of the following risk factors: male, age >70, chronic lung disease, anemia, thrombocytosis, previous VTE, and recent surgery.<sup>215</sup> There is some evidence for early diagnosis that does not affect outcomes.

#### Analyzed literature possible biases

- Many large studies comparing DOACs and LMWH or vitamin K antagonists include less of high-risk cancer patients, which could affect outcomes.
- Rather big amount of pancreatic cancer patients was included in the trials comparing DOACs and LMWH.

#### Suggested next research lines

Differences between various DOACs for the optimal treatment of VTE in cancer patients.

#### Related statement in layman's term for public vein-lymphatic awareness

Venous thrombosis is common in cancer patients, and must be treated with anticoagulation. A specialist should discuss options for anticoagulation.

#### Suggested pertinent extra readings

a) Moik F, Colling M, Mahé I, Jara-Palomares L, Pabinger I, Ay C. Extended anticoagulation treatment for cancer-associated thrombosis-Rates of recurrence and bleeding beyond 6 months: A systematic review. *J Thromb Haemost* 2022;20:619-34.

b) Brandão GMS, Malgor RD, Vieceli T, , Cândido RCF, Inácio JFS, Rodrigues CG, *et al.* A network meta-analysis of direct factor Xa inhibitors for the treatment of cancer-associated venous thromboembolism. *Vascular* 2022;30(1):130-45.

c) Stevens SM, Woller SC, Kreuziger LB, Ounnameaux H, Doerschug K, Geersing GJ, *et al.* Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest* 2021;160:e545-608.

d) Lyman GH, Carrier M, Ay C, Di Nisio M, Hicks LK, Khorana AA, *et al.* American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv* 2021;5:927-74.

### 6. Proper treatment of superficial venous thrombosis

#### Query used for the literature search

("superficial venous thrombosis" OR "superficial thrombophlebitis") AND ("treatment") AND ("meta analysis" OR "Systematic Review" OR "guidelines")

#### Main findings

Superficial venous thrombosis can propagate into the deep venous system and lead to DVT or PE. Patients with a diagnosis of superficial thrombosis should undergo duplex ultrasonography to rule out deep venous thrombosis. This initial ultrasound can also delineate the length of the thrombosis, determine its proximity to the deep venous system, and evaluate venous incompetence for future treatment.<sup>213, 216</sup> Treatments for superficial venous thrombosis are varied, and are aimed at preventing propagation of thrombus and reducing symptoms. In the first three months after diagnosis, rates of VTE range from 1.5% to 6.2%.<sup>213</sup> Randomized clinical trial data support the use of fondaparinux for 45 days for treatment of superficial venous thrombosis of >5 cm in length. This trial only included patients with SVT ≥3 cm from the deep venous junction. This approach has been associated with a rate of DVT and PE of 1.4 per 100 patient-years versus 10.5 per 100 patient-years for no therapy.<sup>217</sup> In patients with SVT closer ≤3 cm from the deep venous junction, therapeutic anticoagulation is recommended to prevent propagation.<sup>213</sup>

Other commonly accepted treatment modalities include low molecular weight heparins, DOACs (rivaroxaban), non-steroid anti-inflammatory drugs (for short-segment superficial thrombosis), surgical ligation of the greater saphenous vein (for proximal lower extremity superficial venous thrombosis), and symptomatic treatment with compression, and mobilization. Treatment with rivaroxaban 10 mg for 45 days is non-inferior to fondaparinux 2.5 mg and can be suggested as alternative for patients who want to avoid injections.<sup>217</sup> However, evidence to support other interventions is limited and of lower quality. Symptomatic management with NSAIDs or compression is unlikely to prevent DVT or PE. Surgical ligation and compression prevent progression and VTE relative to compression alone,<sup>217, 218</sup> but is associated with the highest risk of PE. For superficial venous thrombosis near the deep venous junction, or in patients at high risk of DVT, longer courses of anticoagulation can be considered. Further studies are needed to determine the optimal treatment modality and duration of therapy.<sup>213</sup>

#### Analyzed literature possible biases

Studies of surgical treatments, LMWH, and DOACs often do not consider all relevant clinical endpoints, such as long-term rates of VTE.

#### Suggested next research lines

Role of DOACs, LMWH, and non-steroid anti-inflammatory drugs for treatment of superficial venous thrombosis. Efficacy and safety of endovenous thermal ablation in superficial venous thrombosis in the view of symptomatic relief and VTE rates.

#### Related statement in layman's term for public vein-lymphatic awareness

Superficial venous thrombosis brings the risk of deep venous thrombosis and pulmonary embolism.

#### Suggested pertinent extra readings

a) Beyer-Westendorf J. Controversies in venous thromboembolism: to treat or not to treat superficial vein thrombosis. *Hematology* 2014, the American Society of Hematology Education Program Book 2017;2017:223-30.

b) Kearon C, Akl EA, Comerota AJ, Blaiwas A, Jimenez D, Bounameaux H, *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(Suppl):e419S-94S.

c) Sullivan V, Denk PM, Sonnad SS, Eagleton MJ, Wakefield TW. Ligation versus anticoagulation: treatment of above-knee superficial thrombophlebitis not involving the deep venous system. *J Am Coll Surg* 2001;193:556-62.

### 7. Acute ilio-femoral thrombosis management

#### Query used for the literature search

("ilio-femoral venous thrombosis" OR "proximal DVT" OR "ilio-femoral thrombosis" "femoral thrombosis") AND ("management" OR "treatment") AND ("meta analysis" OR "systematic Review" OR "guidelines")

#### Main findings

Iliofemoral DVT, which refers to DVT in the common femoral veins, iliac veins, and inferior vena cava, is associated with high rates of PTS and complications such as venous ulcers. Iliofemoral DVT is diagnosed using ultrasonography or computed tomography/magnetic resonance venography. Anticoagulation for a minimum of three months is the standard of care for patients with iliofemoral DVT.<sup>219</sup> In recent years, PCDT has emerged as a major treatment modality for ilio-femoral DVT. Three randomized trials (CAVA, CAVENT, and ATTRACT) in patients with lower extremity DVT have helped establish the clinical benefits of PCDT. These studies did not show a decrease in rates of PTS among patients with lower extremity DVT compared to anticoagulation alone. However, subgroup analyses established that PCDT significantly reduces early DVT symptoms and the *severity* of PTS in patients with iliofemoral DVT.<sup>220</sup> Long-term follow-up data also suggested a decrease in the incidence of PTS among patients with iliofemoral DVT (RR 0.82, 95% CI 0.71 to 0.94). PCDT also resulted in greater rates of total clot lysis.<sup>221</sup> There may be a slight increase in bleeding complications with PCDT compared to anticoagulation, so strict criteria should be used to determine patients most likely to benefit from this intervention. Ideal candidates for therapy are younger than 65 with good mobility and low bleeding risk. Patients who undergo PCDT still require anticoagulant therapy to prevent DVT recurrence.<sup>220</sup> More large randomized controlled trials are needed to determine the benefit of catheter-directed thrombolysis in iliofemoral DVT.<sup>221, 222</sup> In recent years, DOACs have become mainstays of DVT therapy because of their efficacy at preventing recurrence and improved safety profile. Because many trials of PCDT occurred before DOACs were in widespread use, PCDT may not compare as favorably to DOACs as to LMWH and vitamin K inhibitors. Endovascular or open surgical thrombectomy is standard of care for phlegmasia cerulea

dolens, a condition characterized by limb-threatening venous occlusion.<sup>220</sup>

#### *Analyzed literature possible biases*

Lack of long-term clinical and quality of life data in studies comparing anticoagulation and catheter-directed thrombolysis. Few large, randomized trials. Many trials comparing catheter directed thrombolysis to warfarin or LMWH, but few comparing to DOACs (lower bleeding and PTS risk).

#### *Suggested next research lines*

Randomized controlled trials to determine which subsets of patients derive the most benefit from catheter-directed thrombolysis. Trials comparing catheter-directed thrombolysis to DOACs.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Special venous catheters can be used by qualified experts to treat specific cases of thrombosis. Guidelines vary among countries and require careful specialist evaluation of the risks and benefits.

#### *Suggested pertinent extra readings*

a) Brenner B, Hull R, Arya R, Beyer-Westendorf J, Douketis J, Elalamy I, *et al.* Evaluation of unmet clinical needs in prophylaxis and treatment of venous thromboembolism in high-risk patient groups: cancer and critically ill. *Thromb J* 2019;17:6.

b) Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315-52.

### **8. Pharmaco-mechanical thrombolysis indications and complications management**

#### *Query used for the literature search*

("pharmaco-mechanical thrombolysis" OR "pharmacomechanical thrombolysis") OR ("deep venous thrombosis" AND "thrombolysis") AND ("meta analysis" OR "systematic review" OR "guidelines")

#### *Main findings*

Catheter-directed thrombolysis may be used alongside endovascular techniques to remove thrombus, such as mechanical thrombectomy, catheter aspiration, balloon maceration, balloon venoplasty, or stenting. This combined approach is known as PMT.<sup>221</sup> Like CDT, PMT is most

commonly used in patients with acute (<14 days since thrombus formation), iliofemoral DVT, good functional status, and low bleeding risk.<sup>223</sup> The best available evidence to support this approach comes from the ATTRACT trial. This trial included 692 patients with acute, proximal DVT and randomized them to either PMT or anticoagulation alone. PMT did not reduce post-thrombotic syndrome but reduced the severity of PTS; in subgroup analyses of iliofemoral DVT patients, PMT also improved venous-specific quality of life.<sup>221</sup> However, meta-analyses have indicated that PMT may slightly reduce rates of post-thrombotic syndrome relative to anticoagulation alone. There was also a small but significant increased risk of bleeding associated with the procedure in the ATTRACT trial (1.7% PCDT vs. 0.3% standard therapy; P=0.049). PCDT also did not significantly reduce recurrent VTE (12.5% PCDT vs. 8.5% standard therapy; P=0.087).<sup>213</sup> Both PMT and CDT are associated with increased rates of complete clot lysis compared to standard anticoagulation, although this has not translated to a reduced risk of PE.<sup>221</sup> There are no significant differences between PMT and CDT in rates of PTS, VTE recurrence, or bleeding events. However, meta-analyses have suggested that PMT is more effective than CDT at reducing severity of PTS, and the clot lysis time and length of hospital stay are also shorter for PMT. High quality evidence is still lacking to support PMT over catheter-directed thrombolysis alone.<sup>223</sup>

#### *Analyzed literature possible biases*

Few studies comparing CDT to PMT, and even fewer comparing to DOACs.

#### *Suggested next research lines*

- Randomized controlled trials comparing CDT to PMT and comparing PMT/CDT to DOACs.
- Need for more research on cutting edge interventional devices for PMT, which have replaced those used in the ATTRACT trial.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Pharmaco-mechanical thrombolysis is clot treatment and removal through a catheter. This treatment is safe in expert hands after proper consideration of the risks and benefits. A careful specialist evaluation must be performed to avoid treatment when not appropriate.

#### *Suggested pertinent extra readings*

- a) Goldhaber SZ, Magnuson EA, Chinnakondepalli KM, Cohen DJ, Vedantham S. Catheter-directed throm-

bolysis for deep vein thrombosis: 2021 update. *Vasc Med* 2021;26:662-9.

- b) Mazzolai L, Ageno W, Alatri A, Bauersachs R, Beccattini C, Brodmann M, *et al.* Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. *Eur J Prev Cardiol* 2022;29:1248-63.

- c) Kahn SR, Julian JA, Kearon C, Gu CS, Cohen DJ, Magnuson EA, *et al.* Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord* 2020;8:8-23.

- d) Comerota AJ. Pharmacologic and Pharmacomechanical Thrombolysis for Acute Deep Vein Thrombosis: Focus on ATTRACT CME. *Methodist DeBakey Cardiovascular Journal* 2018;14:219.

## 9. Anticoagulation therapy indication and contraindication

### Query used for the literature search

“venous thrombosis” OR “venous thromboembolism” OR “VTE” OR “DVT”) AND (“anticoagulation” OR “anti-coagulation”) AND (indication OR contraindication) AND (“meta analysis” OR “systematic review” OR “guidelines”).

### Main findings

Patients with VTE may be anticoagulated with warfarin (vitamin K antagonist), unfractionated heparin, low molecular weight heparin (LMWH), fondaparinux, or direct oral anticoagulants (DOACs). All patients starting anticoagulation should undergo assessment of their complete blood count (CBC), renal and liver function tests, INR, and PTT.<sup>224</sup> DOACs are generally contraindicated in patients with creatinine clearance below 30-15 mL/min or significant liver disease. DOACs are first line medications for DVT and PE.<sup>210</sup> Risk factors for bleeding on anticoagulation include advanced age, bleeding history, cancer, renal or liver failure, thrombocytopenia, stroke, diabetes, anemia, antiplatelet therapy, surgery, falls, alcohol abuse, and non-steroid anti-inflammatory drugs (NSAIDs). Patients with a DVT in the setting of active bleeding can instead receive a retrievable inferior vena cava filter to prevent embolization to the pulmonary arteries.<sup>224</sup> Randomized controlled trials in patients with cancer have clearly demonstrated that low molecular weight heparin (LMWH) is superior to warfarin in this patient population. Similarly, oral factor Xa inhibi-

tors (apixaban, edoxaban, rivaroxaban) have lower risk of recurrent VTE compared to warfarin (RR 0.62) without increased major bleeding events. Notably, edoxaban and rivaroxaban may increase gastrointestinal (GI) bleeding in patients with luminal GI malignancies. Current guidelines for cancer patients recommend treatment by an oral factor Xa inhibitor over LMWH or warfarin, provided the patient is a candidate for anticoagulation and has a creatinine clearance of greater than 30 mL/min. Treatment should continue for at least 6 months. If patients have a recurrent VTE while on anticoagulation, they should either change their dose or change their medication regimen.<sup>210, 225</sup> Critically ill patients are at high risk of VTE and should be treated with LMWH if they develop VTE, as this has a lower risk of heparin-induced thrombocytopenia. If patients are at risk of bleeding, inferior vena cava filters or unfractionated heparin (given its short half-life) can be considered.<sup>225</sup>

### Analyzed literature possible biases

Minimal given large number of adequately powered studies of VTE treatment.

### Suggested next research lines

Role of factor Xa inhibitors in treatment and prevention of VTE.

### Related statement in layman's term for public vein-lymphatic awareness

Before starting anticoagulation (blood thinner) therapy, all patients should have a thorough laboratory workup. Patients with severe kidney disease can use warfarin for anticoagulation. Patients with cancer also need a laboratory workup, and may be eligible for treatment with oral anticoagulants or low molecular weight heparin.

### Suggested pertinent extra readings

- a) Nisly SA, Mihm AE, Gillette C, Davis KA, Tillett J. Safety of direct oral anticoagulants in patients with mild to moderate cirrhosis: a systematic review and meta-analysis. *J Thromb Thrombolysis* 2021;52:817-27.

- b) Ortega-Paz L, Galli M, Capodanno D, Franchi F, Rolini F, Bikdeli B, *et al.* Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials. *Eur Heart J Cardiovasc Pharmacother* 2021;8:677-86.

- c) Mai V, Guay CA, Perreault L, Bonnet S, Bertolotti L, Lacasse Y, *et al.* Extended anticoagulation for VTE: a systematic review and meta-analysis. *Chest* 2019;155:1199-216.

d) Lyman GH, Khorana AA, Kuderer NM, Bohlke K, Lee AY, Arcelus JI, *et al*; American Society of Clinical Oncology Clinical Practice. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31:2189-204.

### 10. DOACS use in acute venous thrombo-embolism management

#### Query used for the literature search

“venous thrombosis” OR “venous thromboembolism” OR “VTE” OR “DVT”) AND (“DOAC” OR “direct oral anticoagulant” OR “direct-acting oral anticoagulant” OR “direct thrombin inhibitor” OR “factor Xa inhibitor”) AND (“treatment” OR “management”) AND (“meta-analysis” OR “systematic review” OR “guidelines”)

#### Main findings

DOACs have been shown to have significantly lower rates of major bleeding compared to vitamin K antagonists or LMWH (RR 0.61, 95% CI: 0.45-0.83).<sup>213</sup> For patients with unprovoked VTE, extended treatment with DOACs results in VTE recurrence rates comparable to vitamin K antagonists.<sup>214</sup> Because these agents are dosed orally once a day and do not require laboratory monitoring, they also have the advantage of being easier for patients to manage. Consequently, they are now widely recommended as first line pharmacotherapy for acute DVT and PE.<sup>213</sup> Prior to starting DOACs, it is always important to evaluate patient’s renal function and to consider possible drug interactions. Patients with unprovoked VTE should be treated with extended DOAC therapy unless bleeding risk is prohibitive. Risk factors for major bleeding on DOACs include age greater than 65, creatinine clearance below 50 mL/min, a history of bleeding, use of antiplatelet therapy, and hemoglobin level less than 100 g/L.<sup>214</sup> Because of the safety profile and ease of administration, DOACs have helped to usher in a shift towards outpatient treatment of DVT. Guidelines recommend outpatient treatment of DVT with DOACs with the following exceptions: patients at risk of massive PE, massive or recurrent VTE, pregnancy, and lack of access to care and social support.<sup>213</sup> Published evidence now favors the safety of outpatient management for patients with low-risk PE as well, provided they meet the above criteria.<sup>214</sup> Meta-analyses of cancer patients with VTE suggest that DOACs may lead to lower rates of VTE recurrence than LMWH (RR 0.65, 95% CI: 0.42-1.01). Meta analyses differ as to whether DOACs have a similar or slightly higher rate of clinically significant bleeding



### 6. VENOUS THROMBOSIS

Venous thrombosis is the formation of an obstruction inside the venous system. When it happens into the leg it can create fragments (emboli) travelling to the lungs and potentially leading to death.

One in four people around the world dies from conditions related to thrombosis. Correct diagnosis and management is fundamental.

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#### VENOUS THROMBOSIS

1. Venous thromboembolism is a blood clot of the veins of the legs (deep venous thrombosis), or lungs (pulmonary embolism). Patients should be informed about their risk factors.
2. Symptoms of a deep venous thrombosis in the arms or legs include pain, swelling, redness, tenderness, fever, bulging veins, and skin discoloration. Symptoms of a pulmonary embolism include chest pain, fast heart rate, coughing up blood, and shortness of breath.
3. Patients who are obese or who have varicose veins are at increased risk of blood clots.
4. Genetic testing may be suggested in a first episode of unprovoked thrombosis for patients under 50 years old, thrombosis with the only risk factor of hormonal therapy or pregnancy, and recurrent VTE if it will affect the further clinical decision on treatment and prophylaxis.
5. Venous thrombosis is common in cancer patients, and must be treated with anticoagulation. A specialist should discuss options for anticoagulation.
6. Superficial venous thrombosis brings the risk of deep venous thrombosis and pulmonary embolism.
7. Special venous catheters can be used by qualified experts to treat specific cases of thrombosis. Guidelines vary among countries and require careful specialist evaluation of the risks and benefits.
8. Pharmaco-mechanical thrombolysis is clot treatment and removal through a catheter. This treatment is safe in expert hands after proper consideration of the risks and benefits. A careful specialist evaluation must be performed to avoid treatment when not appropriate.
9. Before starting anticoagulation (blood thinner) therapy, all patients should have a thorough laboratory workup. Patients with severe kidney disease can use warfarin for anticoagulation. Patients with cancer also need a laboratory workup, and may be eligible for treatment with oral anticoagulants or low molecular weight heparin.
10. Direct oral anticoagulants (DOAC) are the first-line options for most adults for venous thrombo-embolism treatment. Before starting a DOAC, a thorough laboratory workup, including tests for kidney function, should be performed.

Figure 6.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding venous thrombosis.

than LMWH. Regardless, the risk of bleeding is still significant and cancer patients at risk of bleeding should have a careful consideration of risks and benefits before starting DOAC therapy (Figure 6).<sup>212</sup>

#### Analyzed literature possible biases

Minimal due to large number of RCTs and meta-analyses comparing DOACs to other forms of anticoagulation for treatment of VTE.

#### Suggested next research lines

Clinical trials comparing different DOACs to determine the safest and most effective treatments for VTE.

#### Related statement in layman’s term for public vein-lymphatic awareness

Direct oral anticoagulants (DOAC) are the first-line options for most adults for venous thrombo-embolism treat-

ment. Before starting a DOAC, a thorough laboratory workup, including tests for kidney function, should be performed.

### *Suggested pertinent extra readings*

a) Mazzolai L, Ageno W, Alatri A, Bauersachs R, Baccattini C, Brodmann M, *et al.* Second consensus document on diagnosis and management of acute deep vein thrombosis: updated document elaborated by the ESC Working Group on aorta and peripheral vascular diseases and the ESC Working Group on pulmonary circulation and right ventricular function. *Eur J Prev Cardiol* 2022;29:1248-63.

b) Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, *et al.* American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* 2020;4:4693-738.

c) Diaconu N. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41:543-603.

d) Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, *et al.* Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315-52.

## 7. Venous ulcer

### 1. Venous ulcer pathophysiology

#### *Query used for the literature search*

“Venous Ulcer”[Mesh] OR “Varicose Ulcer/pathology”[Mesh] OR “Venous Ulcer/physiopathology”[Mesh] OR “Venous Ulcer/physiopathology”[Mesh]

#### *Main findings*

Venous ulceration represents the severe ending of a not properly managed lower limb venous hypertension, generated by genetic and/or environmental factors. The hemodynamic impairment can be caused by a vein obstruction and/or reflux whose mechanical force is translated into biochemical inflammatory messages leading to tissue damage. The inflammatory process is associated with alteration of the proteolytic activity and with tissue fibrosis and is usually anticipated by the lipodermatosclerosis condition.<sup>226</sup> The vessel wall and valves integrity loss represent a fundamental pathophysiological aspect in the ulceration process, as particularly evident in case of thrombotic processes. Another fundamental player in venous ulceration is the calf pump function, whose decreased performance has been found to be associ-

ated with the same wound presence.<sup>227</sup> Whatever condition is altering the vessel wall elasticity (capacitance), the venous drainage propulsion (conductivity) and/or the vein patency (resistance) might lead to venous hypertension and related ulceration. Genetic mutations can expose the patient to an easier tissue damage and/or to a more cumbersome reparation. In this context, iron metabolism and metalloproteases balance demonstrated a pivotal role.<sup>228</sup> Different pathophysiology theories have been proposed along the years, yet missing complete evidence-based validation. Among these, the venous stasis theory proposed the hypoxia role. The arteriovenous fistula hypothesis reports the shunting of oxygen and nutrients as triggering factor. Fibrin cuff and white blood cell trap theory focused on the venous hypertension role in extravasation of fibrinogen and white blood cell activation, respectively. In conclusion, venous ulcer pathophysiology is still in need of translational medicine investigations to clarify the complex process connecting the venous drainage compromise with the wound generation.<sup>229</sup>

#### *Analyzed literature possible biases*

Reflux time as only hemodynamic parameter to quantify the reflux severity.

#### *Suggested next research lines*

Correlation between hemodynamic impairment objective parameters and inflammatory markers.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Approximately 70% of skin ulcer has a venous origin. 1/5 ulcers have a multi-factorial component that has to be investigated by an expert physician.

#### *Suggested pertinent extra readings*

a) Ortega MA, Fraile-Martínez O, García-Montero C, Álvarez-Mon MA, Chaowen C, Ruiz-Grande F, *et al.* Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. *J Clin Med* 2021;10:3239.

b) Nicolaidis AN. The Most Severe Stage of Chronic Venous Disease: An Update on the Management of Patients with Venous Leg Ulcers. *Advanc Therap* 2020;37(Suppl 1):19-24.

### 2. Venous ulcer proper description

#### *Query used for the literature search*

“Varicose Ulcer/classification”[Mesh] OR “Varicose Ulcer/diagnosis”[Mesh]

*Main findings*

Venous leg ulcers are usually located at the distal part of the leg. A proper description of the lesion must take into account the tissue characteristics, the margin features, the surrounding skin involvement and the possible exudate. Once the site has been identified, the size and shape should be described accurately, taking into consideration also the margin (variable, regular or irregular). The edge can be sloping, tender, everted, punched out.<sup>230</sup> The floor might show necrosis, slough or granulation, while the tissue can be mobile or fixed. The tendency to bleed or not should also be noted. The surrounding skin can present edema, eczema, pigmentation, atrophie blanche and varicosities.<sup>231</sup> The exudate must be properly described as well, and it can be serous, thin, watery: it is usually associated with an inflammatory stage. This condition can be also associated with sanguineous characteristics. In case of thick, yellow/green/brown exudate, an infection must be promptly excluded. The amount of exudate can be gathered by the dressing removal observation and it can be none, scant, minimal (wetting less than 25% of the dressing), moderate (25-75% dressing wetting) or large.<sup>232</sup> The consistency of the same exudate must be noted, together with the odor: two other hints for possible infections. Irregular clinical aspects must immediately lead to the suspect of malignancies.<sup>233</sup>

*Analyzed literature possible biases*

Lack of infected and complicated ulcer inclusion in the majority of published investigations.

*Suggested next research lines*

Real world woundcare data.

*Related statement in layman's term for public vein-lymphatic awareness*

Proper assessment of a venous ulcer must report location, size, shape, surrounding area description, type of floor, edge and discharge.

*Suggested pertinent extra readings*

- a) Hess CT. Venous Ulcer Assessment and Management: Using the Updated CEAP Classification System. *Adv Skin Wound Care* 2020;33:614-5.
- b) Bonkemeyer Millan S, Gan R, Townsend PE. Venous Ulcers: Diagnosis and Treatment. *Am Fam Physician* 2019;100:298-305.
- c) Kirsner RS, Vivas AC. Lower-extremity ulcers: diagnosis and management. *Br J Dermatol* 2015;173:379-90.

**3. Venous ulcer diagnosis work-up**

*Query used for the literature search*

(venous ulcer) AND (diagnosis protocol)

*Main findings*

After detailed history and clinical description of the ulcer, the diagnostic work up must include a venous and arterial echo-color-Doppler, preceded by arterial pulses and ankle-brachial index measurement. This last aspect is fundamental considering around 1/5 of ulcer etiologies are artero-venous. Computed tomography and/or magnetic resonance and/or intravascular ultrasound and/or venography can be helpful particularly in case of need of proximal venous obstruction investigation. In this context, also plethysmography can be of help in providing objective measurements of drainage impairment. Wound swabs or biopsy should be always performed in the suspect of infection or proliferation anomalies, respectively. Advanced assessment may include protease activity as prognostic factor for wound healing, yet more data are needed before confirming the real value of this investigation.<sup>234</sup> Chronic non-healing wounds demonstrated an elevated alkaline environment, suggesting a potential use also of the ulcer PH assessment as prognostic factor. In a similar way, ulcer temperature variation has been taken into consideration, yet, as per the PH, further investigations are needed before recommending their inclusion in the diagnostic work up.<sup>235</sup> Mobility and ankle range of motion are important parameters to be taken into consideration in the general assessment of the venous ulcer patients, particularly considering the related correlation with the wound healing.<sup>236</sup> Considering the impact on the quality of life and the related associated patient depression, psychological evaluation should not be underestimated.<sup>237</sup>

*Analyzed literature possible biases*

Lack of head to head comparison among different diagnostic protocols.

*Suggested next research lines*

Cost effectiveness analysis of the diagnostic options.

*Related statement in layman's term for public vein-lymphatic awareness*

Proper ulcer diagnosis requires detailed anamnesis, clinical visit, arterial and venous ultrasound scanning, lymphatic function assessment, and ankle-brachial index calculation.

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*Suggested pertinent extra readings*

a) Bernatchez SF, Eysaman-Walker J, Weir D. Venous Leg Ulcers: A Review of Published Assessment and Treatment Algorithms. *Adv Wound Care* (New Rochelle) 2022;11:28-41.

b) Hallas S, Nelson A, O’Meara S, Adderley U, Meskill P, Nixon J, *et al.* Development of a core outcome set for venous leg ulceration (CoreVen) research evaluations (protocol). *J Tissue Viability* 2021;30:317-23.

c) Srisuwan T, Inmutto N, Kattipathanapong T, Rerkasem A, Rerkasem K. Ultrasound Use in Diagnosis and Management of Venous Leg Ulcer. *Int J Low Extrem Wounds* 2020;19:305-14.

d) Pernot CC, Zwiers I, Ten Cate-Hoek AJ, Wittens CH. The need for a timely diagnostic workup for patients with venous leg ulcers. *J Wound Care* 2018;27:758-63.

**4. Antibiotics use in wound healing**

*Query used for the literature search*

(antibiotic) AND (venous ulcer)

*Main findings*

Venous leg ulcers are often colonized by several bacterial species, potentially switching into virulent infections, slowing down the wound healing and potentially damaging the general status of the patient. Choosing the proper therapy, while avoiding antibiotic overuse is mandatory to optimize the treatment while counteracting the drug resistance development.<sup>238</sup> Antibiotics should be considered in case of local and systemic symptoms and signs of infection, such as pain, erythema, tenderness, temperature increase, chills. Proper culture should guide the targeted therapy. A Cochrane meta-analysis reported how cadexomer iodine and silver dressings can be useful in this context, yet high grade evidence is missing, together with the related cost-effectiveness analysis.<sup>239</sup> A recent investigation focused on the comparison among systemic versus local versus combined systemic and local antibiotic therapy in venous ulcers. The combination of systemic and local showed higher healing velocity, lower recurrence rate, lesser risk of septicemia, lesser need of surgical intervention, shorter stay and better cost-effectiveness. Nevertheless, antibiotic resistance was up to 6 times higher. Further large studies are needed to confirm this finding and lead to high recommendations.<sup>240</sup> Indeed, another recent publication demonstrated how the venous leg ulcer healing time is prolonged by each subsequent bacterial strain, independently from the systemic antibiotic use.<sup>241</sup>

*Analyzed literature possible biases*

Heterogeneity in investigated ulcer bacterial load.

*Suggested next research lines*

Multicenter studies on best antibiotic protocols in complicated ulcers.

*Related statement in layman’s term for public vein-lymphatic awareness*

Culturing and systemic antibiotics are indicated only in presence of signs and symptoms of infection. Antimicrobials are not recommended in only contaminated wounds.

*Suggested pertinent extra readings*

a) Cwajda-Białasik J, Mościcka P, Jawień A, Szewczyk MT. Microbiological Status of Venous Leg Ulcers and Its Predictors: A Single-Center Cross-Sectional Study. *Int J Environ Res Public Health* 2021;18:12965.

b) Di Domenico EG, Farulla I, Prignano G, Gallo MT, Vespaziani M, Cavallo I, *et al.* Biofilm is a Major Virulence Determinant in Bacterial Colonization of Chronic Skin Ulcers Independently from the Multidrug Resistant Phenotype. *Int J Mol Sci* 2017;18:1077.

c) Rahim K, Saleha S, Zhu X, Huo L, Basit A, Franco OL. Bacterial Contribution in Chronicity of Wounds. *Microb Ecol* 2017;73:710-21.

d) Moore K, Hall V, Paull A, Morris T, Brown S, McCulloch D, *et al.* Surface bacteriology of venous leg ulcers and healing outcome. *J Clin Pathol* 2010;63:830-4.

**5. Biopsy in ulcer management**

*Query used for the literature search*

(biopsy) AND (venous ulcer)

*Main findings*

Skin biopsies help to find a correct diagnosis in unclear or non-healing cases. Malignancy in chronic ulcers has to be differentiated in primary malignant ulcers because a chronic wound may transform into a malignant tumor. The prevalence of malignancy in chronic leg ulcers in the literature ranges from 2.0% to 2.8% in retrospective analyses and 4% to 10.4% in prospective studies. The two most common types of ulcerating skin tumors are basal cell carcinoma and squamous cell carcinomas. Biopsy may reveal cutaneous leishmaniasis and Pyoderma gangrenosum. Malignant tumors as a cause of chronic leg or foot ulcers are often overlooked. Initial misdiagnoses could lead to a delay in appropriate therapy man-

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agement. A biopsy should be performed in the absence of healing tendency after six weeks of treatment.<sup>242</sup> An everted edge and excessive granulation have been found to be significantly more frequently associated with malignancies. Non-vascular ulcer cause usually are also associated to a vascular involvement, suggesting the need to perform a skin biopsy in case of suspect, even in the presence of a vascular disease.<sup>243</sup> In properly trained centers, skin biopsy demonstrated to be safe, presenting as main complication a dull pain and a rare risk of bleeding (0.23%).<sup>244</sup> Proper standardization and global validation of the biopsy technique is still lacking in the literature.<sup>245</sup>

*Analyzed literature possible biases*

Lack of standardization in the biopsy protocols reported in the literature.

*Suggested next research lines*

Head-to-head comparison among different biopsy protocols.

*Related statement in layman's term for public vein-lymphatic awareness*

In case of atypical appearance, a biopsy must be performed to exclude malignancy, vasculitis or arterial sclerosis.

*Suggested pertinent extra readings*

- a) Schneider C, Stratman S, Kirsner RS. Lower Extremity Ulcers. Med Clin North Am 2021;105:663-79.
- b) Alam W, Hasson J, Reed M. Clinical approach to chronic wound management in older adults. J Am Geriatr Soc 2021;69:2327-34.
- c) Toussaint F, Erdmann M, Berking C, Erfurt-Berge C. Malignant Tumors Presenting as Chronic Leg or Foot Ulcers. J Clin Med 2021;10:2251.
- d) Bowers S, Franco E. Chronic Wounds: Evaluation and Management. Am Fam Physician 2020;101:159-66.

**6. Compression protocols in venous ulcer patients**

*Query used for the literature search*

(graduated compression) AND (venous ulcer)

*Main findings*

International guidelines globally recognize the pivotal role of appropriate compression in venous ulcer healing.<sup>7</sup> A recent Cochrane review reported that bandages or graduated compression stockings are associated with a probable quicker and more effective wound healing.

The potential benefit of their use has been shown also in pain control and disease-specific quality of life. Adverse effects and cost-effectiveness of compression in this setting remain unclear.<sup>246</sup> Appropriate compression is also considered fundamental for recurrence management: non-compliance to compression has been associated with up to 70% recurrence rate.<sup>247</sup> A recent publication on venous ulcer patients demonstrated the non-inferiority in healing rate, as well as the competitiveness in cost-efficacy, of a specific adjustable compression wrap versus inelastic bandaging.<sup>248</sup> The possibility of readjusting the compression dose along time represents a benefit considering the bandaging interface pressure variability.<sup>249</sup> Intermittent pneumatic compression was reported to potentially improve wound healing rate compared to no compression, but its alternative role to compression bandages remains unclear.<sup>250</sup> Literature demonstrating the best compression modality, timing and dosing is still missing.

*Analyzed literature possible biases*

Lack of interface pressure measurement in several studies.

*Suggested next research lines*

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

*Related statement in layman's term for public vein-lymphatic awareness*

Compression is the mainstay of ulcer healing and can be performed by proper bandage, graduated compression stocking and adjustable compression use, following expert prescription and application. In difficult healing cases, intermittent pneumatic compression can provide a valuable option.

*Suggested pertinent extra readings*

- a) Alvarez OM, Markowitz L, Parker R, Wendelken ME. Faster Healing and a Lower Rate of Recurrence of Venous Ulcers Treated With Intermittent Pneumatic Compression: Results of a Randomized Controlled Trial. Eplasty 2020;20:e6.
- b) Mościcka P, Szewczyk MT, Cwajda-Białasik J, Jawień A. The role of compression therapy in the treatment of venous leg ulcers. Adv Clin Exp Med 2019;28:847-52.
- c) De Carvalho MR, Peixoto BU, Silveira IA, Oliveira BG. A Meta-analysis to Compare Four-layer to Short-stretch Compression Bandaging for Venous Leg Ulcer Healing. Ostomy Wound Manage 2018;64:30-7.

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## 7. Venous reflux suppression best strategy in venous ulcer patients

### *Query used for the literature search*

((venous ulcer) AND (reflux)) AND (therapy) ((“Varicose Ulcer”[Mesh]) AND “Varicose Ulcer/surgery”[Mesh])

### *Main findings*

Early endovenous thermal suppression of the venous reflux leading to ulceration demonstrated to be beneficial for a faster healing and associated with a longer post-procedural ulcer-free time. In a 3 year time, early endovenous ablation was reported to be highly likely to be also cost-effective.<sup>251</sup> Recent data show that simultaneous treatment of incompetent perforating veins at the time of the radiofrequency saphenous ablation improves venous ulcer healing.<sup>252</sup> In case of wound healing failure after superficial and perforator reflux treatment, the presence of hemodynamically significant ilio-caval stenosis should be assessed in detail and eventually treated.<sup>253</sup> The use of endovenous cyanoacrylate glue (Venaseal) demonstrated to be safe and effective in saphenous vein ablation and ulcer healing. Further data are needed, in particular in case of infected ulcers, before providing high grades of recommendation in its use in ulcer patients.<sup>254</sup> A global survey demonstrated the need of improving wound care management by creating validated and universally applied management protocols, overcoming the limits coming from the different economic and health services resources, including proper public and health-professionals education.<sup>255</sup>

### *Analyzed literature possible biases*

Heterogeneity in ulcer type inclusion.

### *Suggested next research lines*

Head to head comparison among different reflux suppression techniques.

### *Related statement in layman's term for public vein-lymphatic awareness*

Early restoration of superficial venous reflux is indicated in venous ulcer management.

### *Suggested pertinent extra readings*

a) Ojha V, Kumar S. Current strategies for endovascular management of varicose veins: An updated review of superficial ablation technologies. *Phlebology* 2022;37:86-96.

b) Salim S, Heatley F, Bolton L, Khatri A, Onida S, Davies AH. The management of venous leg ulceration post

the EVRA (early venous reflux ablation) ulcer trial: Management of venous ulceration post EVRA. *Phlebology* 2021;36:203-8.

c) Goldschmidt E, Schafer K, Lurie F. A systematic review on the treatment of nonhealing venous ulcers following successful elimination of superficial venous reflux. *J Vasc Surg Venous Lymphat Disord* 2021;9:1071-6.e1.

d) Lurie F. Advanced Stages of Chronic Venous Disease: Evolution of Surgical Techniques and Advantages of Associated Medical Treatment. *Adv Ther* 2020;37(Suppl 1):6-12.

## 8. Advanced wound dressings evidence-based need in woundcare

### *Query used for the literature search*

(dressing) AND (venous ulcer)

### *Main findings*

A 2018 Cochrane network meta-analysis reviewed 78 randomized comparative trials on the use of advanced dressings for venous ulcer healing. The conclusion states that more research is needed to determine whether particular dressings or topical agents improve the probability of healing of venous leg ulcers. It also focuses on the main outcome parameter of the review being the complete ulcer healing, while other variable should be taken into considerations, such as patient preference, quality of life and cost-effectiveness.<sup>239</sup> A recent review reported a great variation in clinical and cost efficacy of advanced wound care matrices. Four randomized comparative trials showed significant improvement over standard therapy by using bilayer skin substitute, dehydrated human amnion/chorion membrane, extracellular wound matrix and advanced matrix. The inconsistency in the related studies methodology was pointed out, urging more appropriate data collection on the topic.<sup>256</sup> From 2014 to 2021, 43 randomized comparative trials investigated the use of topical products for venous ulcer healing. A review grouping their results demonstrated how, despite the many products commercialized, there is no strong evidence to support their use, urging properly conducted studies on the topic.<sup>257</sup> The same wound cleansing specifics remain uncertain, with insufficient evidence to support the use of polyhexamethylene biguanide compared with saline solution, aqueous oxygen peroxide compared with sterile water; propyl betaine and polihexanide compared with a saline solution or octenidine dihydrochloride/phenoxethanol compared with Ringer's solution makes any difference.<sup>258</sup>

*Analyzed literature possible biases*

Lack of properly conducted randomized comparative trials on homogeneous study populations.

*Suggested next research lines*

Multi-center head-to-head comparisons, including complicated ulcers.

*Related statement in layman's term for public vein-lymphatic awareness*

Advanced wound dressings might improve ulcer healing process, but no strong evidence is supporting one product over another.

*Suggested pertinent extra readings*

a) Verdú-Soriano J, de Cristino-Espinar M, Luna-Morales S, Dios-Guerra C, Caballero-Villarraso J, Moreno-Moreno P, *et al.* Superiority of a Novel Multifunctional Amorphous Hydrogel Containing *Olea europaea* Leaf Extract (EHO-85) for the Treatment of Skin Ulcers: A Randomized, Active-Controlled Clinical Trial. *J Clin Med* 2022;11:1260.

b) Emmert S, Pantermehl S, Foth A, Waletzko-Hellwig J, Hellwig G, Bader R, *et al.* Combining Biocompatible and Biodegradable Scaffolds and Cold Atmospheric Plasma for Chronic Wound Regeneration. *Int J Mol Sci* 2021;22:9199.

c) Massand S, Lewcun JA, LaRosa CA. Clinical and cost efficacy of advanced wound care matrices in the treatment of venous leg ulcers: a systematic review. *J Wound Care* 2021;30:553-61.

d) Holmes SP, Rivera S, Hooper PB, Slaven JE, Que SK. Hydrocolloid dressing *versus* conventional wound care after dermatologic surgery. *JAAD Int* 2021;6:37-42.

**9. Skin grafting, negative pressure therapy, stem cells therapy**

*Query used for the literature search*

(skin grafting) AND (venous ulcer); (negative pressure) AND (venous ulcer) ; (stem cells) AND (venous ulcer)

*Main findings*

The pivotal initial treatment of venous ulcers includes wound care, debridement, appropriate life-style and compression. In case of delayed healing, after 4-6 weeks, advanced options might be taken into consideration, among which skin grafting, negative pressure therapy and stem cells from adipose tissue or placenta injection. Autologous platelet-rich plasma and other blood derived components

are proposed as well. All these options, while potentially beneficial, are lacking solid scientific data for which their indication is still left to the evaluation of the single case and in need of proper evidence-based validation.<sup>259</sup> Skin substitutes showed potentials in reducing mortality and lessen morbidity while improving quality of life. Yet no commercially available products have recent sufficient scientific validation to be recommended, up to the knowledge of the authors.<sup>260</sup> Innovative therapeutic options of this kind are still in need of properly conducted randomized comparative trials.<sup>261</sup> A 2022 review identified just four papers, of which just one randomized comparative trial, investigating the use of adipose derived stem cells in venous ulcer healing. This therapeutic approach may enhance ulcer healing and appears to be safe on initial reports. Nevertheless, more solid publications are needed, including the safety profile, before recommending this wound therapy.<sup>262</sup> Also for negative pressure therapy use in venous ulcer healing there is limited rigorous evidence. Mild evidence suggest it can reduce the healing time, yet the result is biased by the very specific lesions type included in the investigations.<sup>263</sup>

*Analyzed literature possible biases*

Specific ulcer types evaluation with limited number of cases.

*Suggested next research lines*

Large multicenter randomized trial on head-to-head comparison among the different treatments.

*Related statement in layman's term for public vein-lymphatic awareness*

Skin grafting, Negative Pressure Therapy, Stem cells therapy can be valuable options in specific cases assessed by experts, but more scientific evidence is needed for supporting their use in ulcer healing.

*Suggested pertinent extra readings*

a) Falanga V, Grada A, Otero-Vinas M, Lin X, Yufit T, Fiore D, *et al.* Autologous Cultured Bone Marrow-Derived Mesenchymal Stem Cells in a Fibrin Spray to Treat Venous Ulcers: A Randomized Controlled Double-Blind Pilot Study. *Surg Technol Int* 2022;40:47-54.

b) Kirsner RS, Zimnitsky D, Robinson M. A prospective, randomized, controlled clinical study on the effectiveness of a single-use negative pressure wound therapy system, compared to traditional negative pressure wound therapy in the treatment of diabetic ulcers of the lower extremities. *Wound Repair Regen* 2021;29:908-11.

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c) Dong Y, Yang Q, Sun X. Comprehensive Analysis of Cell Therapy on Chronic Skin Wound Healing: A Meta-Analysis. *Hum Gene Ther* 2021;32:787-95.

d) Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix *Versus* Conventional Care for the Treatment of Venous Leg Ulcers. *Wounds* 2019;31:68-74.

## 10. Venous ulcer recurrence management

*Query used for the literature search*

(recurrence) AND (venous ulcer)

### Main findings

Despite the many advancements in the patho-physiology understanding and in the available therapeutic tools, venous ulcer recurrence remains a significant burden, with data reporting around 50% of incidence with 230 days

from healing mean onset.<sup>264</sup> The complexity and the multifactorial aspects of the severe venous hypertension require proper management not only before and during the wound healing process, but also and equally in the post-treatment phase, when compression, validated venous active drugs, physical exercise and life-style in general can become of paramount importance.<sup>265</sup> Even in case of successful superficial venous reflux suppression, persistent ulceration has been reported from 2.3% at 2 years to 21.1% at 1 year. Repeated refluxing vein ablation led to a successful healing in 50% of cases, while 100% cases were solved by four-layer compression and 90% by compression and ablation of incompetent perforating veins. In case of ulcer recurrence it is fundamental to ascertain the absence of reflux in the superficial/deep/perforator systems. Post-thrombotic and/or central obstructions hemodynamic consequences must also be excluded.<sup>266</sup> Patient disease awareness and related education have a fundamental role in the everyday practice observation. Yet, further studies are needed to identify the evidence-based real impact of the patient engagement, focusing in particular on the patient reported outcomes and cost-effectiveness measures (Figure 7).<sup>267</sup>

### Analyzed literature possible biases

Lack of patient follow-up in outpatient clinics and adherence to treatment after healing.

### Suggested next research lines

Real world data registry.

### Related statement in layman's term for public vein-lymphatic awareness

Ulcer recurrence remains frequent. Proper compression and management can reduce the risk of ulcer reappearance. A specialist follow-up is needed.

### Suggested pertinent extra readings

a) Rosenberg M, Fagerström C, Tuvesson H, Lindqvist G. Daily life after healing of a venous leg ulcer: A life-world phenomenological study. *Int J Qual Stud Health Well-being* 2022;17:2054080.

b) Qiu Y, Osadnik CR, Team V, Weller CD. Effects of physical activity as an adjunct treatment on healing outcomes and recurrence of venous leg ulcers: A scoping review. *Wound Repair Regen* 2022;30:172-85.

c) Bernatchez SF, Eysaman-Walker J, Weir D. Venous Leg Ulcers: A Review of Published Assessment and Treatment Algorithms. *Adv Wound Care (New Rochelle)* 2022;11:28-41.

## 7. VENOUS ULCER

A leg skin lesion caused by venous disease (ulcer) is far more frequent than what usually thought, involving up to 3% of the population. Proper awareness and management is mandatory, also to avoid complications significantly affecting the quality of life. An effective collaboration between the expert physicians, health-professionals and the same patient is the key to prevention and eventually prompt healing of the lesion. Together with the ten evidence-based statements reported below, further insight is available here:

[www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)



### VENOUS ULCER

1. Approximately 70% of skin ulcer has a venous origin. 1/5 ulcers have a multifactorial component that has to be investigated by an expert physician.
2. Proper assessment of a venous ulcer must report location, size, shape, surrounding area description, type of floor, edge & discharge.
3. Proper ulcer diagnosis requires detailed anamnesis, clinical visit, arterial & venous ultrasound scanning, lymphatic function assessment, and ankle-brachial index calculation.
4. Culturing and systemic antibiotics are indicated only in presence of signs and symptoms of infection. Antimicrobials are not recommended in only contaminated wounds.
5. In case of atypical appearance, a biopsy must be performed to exclude malignancy, vasculitis or arterial sclerosis.
6. Compression is the mainstay of ulcer healing and can be performed by proper bandage, graduated compression stocking and adjustable compression use, following expert prescription and application. In difficult healing cases, intermittent pneumatic compression can provide a valuable option.
7. Early restoration of superficial venous reflux is indicated in venous ulcer management.
8. Advanced wound dressings might improve ulcer healing process, but no strong evidence is supporting one product over another.
9. Skin grafting, Negative Pressure Therapy, Stem cells therapy can be valuable options in specific cases assessed by experts, but more scientific evidence is needed for supporting their use in ulcer healing.
10. Ulcer recurrence remains frequent. Proper compression and management can reduce the risk of ulcer reappearance. A specialist follow up is needed.

Figure 7.—Public vein-lymphatic awareness evidence-based statements in layman's terms regarding venous ulcer.

d) Goldschmidt E, Schafer K, Lurie F. A systematic review on the treatment of nonhealing venous ulcers following successful elimination of superficial venous reflux. *J Vasc Surg Venous Lymphat Disord* 2021;9:1071-6.e1.

e) Finlayson K, Wu ML, Edwards HE. Identifying risk factors and protective factors for venous leg ulcer recurrence using a theoretical approach: A longitudinal study. *Int J Nurs Stud* 2015;52:1042-51.

## 8. Venous active drugs

### 1. Certified and validated venous active drugs

#### *Query used for the literature search*

((venous insufficiency[MeSH Terms]) AND (active drug OR phlebotonic)) NOT (thrombo\*[MeSH Terms]) NOT (ischemia)

#### *Main findings*

“Quackery” is a term indicating “promotion of products that do not work or have not been proven to work.” The large diffusion of dietary supplements has exposed the public to the risk of false claims in terms of the related health benefit associated with different components assumption.<sup>268</sup> Scientific organizations should be the first line of opposition toward such issue, promoting proper research and avoidance of confounding commercials.<sup>269</sup> VAD could be defined as a group of natural or synthetic substances counteracting the inflammation and vessel dilation associated with venous reflux, leading to a potential clinical benefit, in an evidence-based context. Among the natural ones, four main categories can be identified:

- benzopyrones (alpha, such as coumarin and dicumarol, or gamma, also known as “flavonoids”, such as miconized purified flavonoid fraction, diosmine, kaempferol, diosmetin, quercetin, rutin, rutosides, hesperidin, oxerutine);
- glycosaminoglycans (sulodexide);
- saponins (such as escin, also known as horse-chestnut, ruscus, Centella asiatica);
- other plant extracts:
  - anthocyanosides: blueberry extract, protoescigenin, barringtogenol, cryptoeschin;
  - proanthocyanidins (maritime pine tree extract), grape seed extracts;
  - ginkgo biloba.

The natural or synthetic origin does not implicate differences in safety or efficacy. Among the main synthetic ones there are calcium dobesilate, benzarone and

naftazone. The safety profile of these products has been documented as high, with mainly gastro-intestinal side effects. Insomnia, drowsiness and headaches have been reported as well, together with transient agranulocytosis (the latter for calcium dobesilate use).<sup>270</sup> Proper specialist customized prescription is of fundamental importance. Analysis of the available literature and guidelines pointed out the importance of not grouping the different drugs all together in a single recommendation category in order to avoid evidence-based findings “dilution”. Indeed, different drugs demonstrated different clinical benefit by means of different scientific works. Also for this reason, a scientifically aware prescription and use must be promoted.<sup>7</sup>

#### *Analyzed literature possible biases*

Lack of correlation between objective haemodynamic and quality of life parameters.

#### *Suggested next research lines*

- Evidence based data production on supplements.
- Quality of life and cost-effectiveness in VAD use.

#### *Related statement in layman's term for public vein-lymphatic awareness*

An excess of products in the market are claiming activities on the venous-lymphatic system that are not properly scientifically demonstrated. Relying on the available evidence and research as well as expert physicians advise is mandatory.

#### *Suggested pertinent extra readings*

a) Mansilha A, Gianesini S, Ulloa JH, Lobastov K, Wang J, Freitag A, *et al.* Pharmacological treatment for chronic venous disease: an umbrella review of systematic reviews. *Int Angiol* 2022;41:249-57.

b) De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, *et al.* European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg* 2022;63:184-267.

c) Pompilio G, Nicolaidis A, Kakkos SK, Integlia D. Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease. *Phlebology*. 2021;36:695-709.

d) Martinez-Zapata MJ, Vernooij RW, Stein AT, Moreno RM, Vargas E, *et al.* Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev* 2020;11: CD003229.

## 2. MPFF evidence-based use in chronic venous disease management

### Query used for the literature search

(micronized purified flavonoid fraction) OR (diosmin [MeSH Terms])

### Main findings

MPFF consists of diosmin 90% and 10% of an additional flavonoid fraction (i.e., diosmetin, hesperidin, linarin, isorhoifolin). The micronization is a method to reduce the particles diameter with the aim of improving intestinal absorption. MPFF has been the most investigated VAD currently on the market and it is positioned as the most recommended in several international guidelines.<sup>7</sup> It shows an anti-inflammatory mechanism of action, including endothelial phenotype expression modification with reduction of capillary permeability and leukocyte adhesion.<sup>270</sup> Clinically, MPFF demonstrated its efficacy in chronic venous disease signs and symptoms management in all the disease stages. In particular, it showed control of CVD related pain, heaviness, swelling, functional discomfort, cramps, paresthesia, burning, pruritus, redness, skin changes and edema. Its use was also associated with an improvement in the patient quality of life. Recent data confirmed its potentials also in post-venous procedural pain relief, hematoma and hyperpigmentation reduction, CVD related symptoms improvement. MPFF demonstrated to facilitate healing of venous leg ulcers.<sup>271</sup> Preliminary data also suggest its potentials in pelvic venous reflux associated symptoms management.<sup>168</sup> The above-mentioned results refer specifically to MPFF use. Further studies are needed to properly compare MPFF versus non-micronized diosmin, as well as the role of eventual prescription variations in terms of dosages and timing. Caution must be used in the comparison of different VAD effects on CVD patients, avoiding grouping different trials with different quality of evidence together. Properly conducted randomized comparative trials and meta-analysis should be taken into consideration before proceeding with guidelines or consensus document recommendations. It must be strongly emphasized that the results of the MPFF studies should not be directly extrapolated to the non-micronized diosmin group which is currently available in many countries in the form of drugs or dietary supplements. The evidence about these molecules (non-micronised diosmin) remains limited.

### Analyzed literature possible biases

Lack of correlations between hemodynamic and quality of life outcomes.

### Suggested next research lines

Timing and dosage protocols and related clinical and cost-effectiveness.

### Related statement in layman's term for public vein-lymphatic awareness

Micronized purified flavonoid fraction (MPFF) demonstrated to be potentially beneficial in all chronic venous disease clinical classes, improving several signs and symptoms.

### Suggested pertinent extra readings

a) Gerges SH, Wahdan SA, Elsherbiny DA, El-Demerdash E. Pharmacology of Diosmin, a Citrus Flavone Glycoside: An Updated Review. *Eur J Drug Metab Pharmacokin* 2022;47:1-18.

b) Cazaubon M, Benigni JP, Steinbruch M, Jabbour V, Gouhier-Kodas C. Is There a Difference in the Clinical Efficacy of Diosmin and Micronized Purified Flavonoid Fraction for the Treatment of Chronic Venous Disorders? Review of Available Evidence. *Vasc Health Risk Manag* 2021;17:591-600.

c) Lurie F. Advanced Stages of Chronic Venous Disease: Evolution of Surgical Techniques and Advantages of Associated Medical Treatment. *Adv Ther* 2020;37(Suppl 1):6-12.

d) Mansilha A. Early Stages of Chronic Venous Disease: Medical Treatment Alone or in Addition to Endovenous Treatments. *Adv Ther* 2020;37(Suppl 1):13-8.

## 3. Sulodexide evidence-based use in chronic venous disease management

### Query used for the literature search

(sulodexide) AND ((vein) OR (venous))

### Main findings

Sulodexide is a drug made by a fast-moving heparin fraction and by a dermatan sulphate fraction. It demonstrated an anti-inflammatory effect providing endothelium protection and permeability regulation, coagulation balance and basal tone action. Clinical trials demonstrate its potential benefits in peripheral arterial disease, diabetic nephropathy and retinopathy, post-myocardial infarction, recurrent deep venous thrombosis, post-thrombotic syndrome and CVD. A recent review on sulodexide demonstrated its capability to decrease the intensity of pain, cramps, heaviness, oedema, together with a reduction in inflammatory mediators in patients with CVD.<sup>272</sup> Another literature revision concluded the drug is at least

as effective as pentoxifylline and MPFF in venous ulcer healing. Randomized comparative and head-to-head studies are needed to provide solid recommendations all along the CVD spectrum.<sup>273</sup> Sulodexide demonstrated to reduce the risk of unprovoked venous thromboembolism recurrence, with no increase in bleeding risk. Future studies are needed to assess the value of the drug in the periprocedural thromboprophylaxis context.<sup>35</sup> Preliminary data showed the possibility of reducing post-sclerotherapy pigmentation following the use of sulodexide.<sup>274</sup> This drug vasculoprotective action was shown also in COVID induced endotheliopathy, leading to a reduced need of hospital admission and oxygen administration. Patients undergoing sulodexide treatment showed no differences in thrombo-embolic events, major bleeding or mortality.<sup>275</sup>

#### Analyzed literature possible biases

Head-to-head studies on sulodexide impact on CVD signs and symptoms.

#### Suggested next research lines

- Sulodexide features in venous periprocedural thromboprophylaxis.
- RCT on CVD related signs and symptoms.

#### Related statement in layman's term for public vein-lymphatic awareness

Sulodexide demonstrated to significantly control chronic venous disease signs and symptoms, to favor venous ulcer healing, to reduce the risk of thrombotic recurrence in specific context, to potentially reduce the impact of COVID-induced inflammation.

#### Suggested pertinent extra readings

a) Asiiwwe IG, Pushpakom SP, Turner RM, Kolamunage-Dona R, Jorgensen AL, Pirmohamed M. Cardiovascular drugs and COVID-19 clinical outcomes: a systematic review and meta-analysis of randomized controlled trials. *Br J Clin Pharmacol* 2022;88:3577-99.

b) Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. *Wounds* 2020;32:195-207.

c) Bignamini AA, Matuška J. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta-analysis. *Adv Ther* 2020;37:1013-33.

d) Gianesini S, Onida S, Obi A, Baccellieri D, Bissacco D, Borsuk D, *et al.* Global guidelines trends and controversies in lower limb venous and lymphatic disease. *Phlebology* 2019;34:4-66.

• e) Andreozzi GM, Bignamini AA, Davi G, Palareti G, Matuška J, Holý M, *et al.*; SURVET Study Investigators. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study. *Circulation* 2015;132:1891-7.

#### 4. Ruscus evidence-based use in chronic venous disease management

##### Query used for the literature search

(ruscus) OR (cyclo 3)

##### Main findings

*Ruscus aculeatus* extract contains saponins, flavonoids, sterols, tyramine, cumarine, triterpenes and benzofuran. *Ruscus* extract can be used alone or in combination with other molecules including the flavonoid HMC and ascorbic acid. *Ruscus* extract possess venotonic activity related to the direct activation of  $\alpha 1$ - and  $\alpha 2$  adrenergic receptors located in the smooth muscle cells as well as an indirect effect *via* the noradrenalin release. In the lab studies an increase of the lymphatic tone was also documented. Among other important proprieties of *ruscus* extract, the microcirculation protection (including, endothelial cell protection, inhibition of their activation and endothelial layer permeability decrease), as well as inflammation reduction should also be mentioned. As documented in the recent studies the anti-inflammatory and protective effects of *ruscus* on the capillaries are, at least in part, mediated *via* muscarinic receptors. HMC used in the combined drugs containing *ruscus* extract potentially lowers the capillary filtration rate and has vasoconstrictive properties (additive to *ruscus* own proprieties).<sup>276</sup> According to the systemic review and meta-analysis of 10 RCTs *ruscus* extract in combination with HMC and vitamin C shows significant efficacy on CVD symptom improvement, including pain, heaviness, fatigue, feeling of swelling, cramps, itching and paresthesia. Regarding objective assessment of leg oedema, *ruscus* significantly reduced ankle circumference as well as foot volume compared with placebo.<sup>277</sup> *Ruscus* extract + HMC + ascorbic acid was positioned among the drugs with high level of evidence in regard to the CVD symptoms reduction as well as leg swelling decrease.<sup>278</sup> Despite the successful use of *ruscus* treatment in the patients with various advancing stages of CVD, in the range from C0s to C4, there is lack of high quality evidence on the clinical efficacy of *ruscus* and *ruscus* containing drugs in VLU healing.<sup>279</sup>



*Analyzed literature possible biases*

- Heterogeneity of the studies performed with ruscus extract only as well as with ruscus in combination with HMC and vitamin C.
- Limited data compared to MPFF use through all the CVD spectrum.

*Suggested next research lines*

- Timing and dosage protocols in early and advanced stages of CVD.
- Head-to-head comparison with the most validated VADs.

*Related statement in layman's term for public vein-lymphatic awareness*

Ruscus aculeatus demonstrated to be potentially beneficial in chronic venous disease related symptoms improvement as well as in chronic venous disease oedema treatment. More evidence is needed to position it as the most recommended drug.

*Suggested pertinent extra readings*

- de Almeida Cyrino FZ, Balthazar DS, Sicuro FL, Bouskela E. Effects of venotonic drugs on the microcirculation: Comparison between Ruscus extract and micronized diosmine1. Clin Hemorheol Microcirc 2018;68:371-82.
- Carpentier P, Allaert FA, Chudek J, Mosti G. Phlebotonic and compression stocking therapy in venous edema management: an overview of recent advances with a focus on Cyclo 3 Fort® and progressive compression stockings. Womens Health (Lond) 2013;9:325-33.
- Jawien A, Bouskela E, Allaert FA, Nicolaïdes AN. The place of Ruscus extract, hesperidin methyl chalcone, and vitamin C in the management of chronic venous disease. Int Angiol 2017;36:31-41.
- Raully-Lestienne I, Heusler P, Cussac D, Lantoin-Adam F, de Almeida Cyrino FZ, Bouskela E. Contribution of muscarinic receptors to in vitro and in vivo effects of Ruscus extract. Microvasc Res 2017;114:1-11.

**5. Rutosides evidence-based use in chronic venous disease management**

*Query used for the literature search*

(rutosides) AND ((vein) OR (venous))

*Main findings*

Rutosides are derived from horse chestnut whose active component is escin. Escin demonstrated an anti-proteolytic activity on the capillary wall, leading to a fluid leakage counteraction. Its effect demonstrated to reduce pain, heaviness, cramps and swelling sensation. Methodology biases related to the homogeneity of the study population, lack of blinding and different confounders.<sup>273</sup> Rutosides benefit on ulcer healing has recently been questioned by a dedicated revision of the literature.<sup>280</sup> Some data suggest a potential short-term benefit of Rutosides in post-thrombotic syndrome symptoms, but a dedicated Cochrane analysis highlighted the need of proper data collection before recommending this drug use in the symptomatology prevention context. The analysis provided no evidence to support the use of rutosides also in the treatment of post-thrombotic syndrome.<sup>281</sup> A 2020 Cochrane meta-analysis included 28 studies on Rutosides concluding that rutosides probably improve oedema, volume of the leg and pain. Very limited action was demonstrated in ankle perimeter reduction and ulcer healing. Very low evidence support its use for reducing heaviness, cramps, itching, and paraesthesia.<sup>282</sup>

lytic activity on the capillary wall, leading to a fluid leakage counteraction. Its effect demonstrated to reduce pain, heaviness, cramps and swelling sensation. Methodology biases related to the homogeneity of the study population, lack of blinding and different confounders.<sup>273</sup> Rutosides benefit on ulcer healing has recently been questioned by a dedicated revision of the literature.<sup>280</sup> Some data suggest a potential short-term benefit of Rutosides in post-thrombotic syndrome symptoms, but a dedicated Cochrane analysis highlighted the need of proper data collection before recommending this drug use in the symptomatology prevention context. The analysis provided no evidence to support the use of rutosides also in the treatment of post-thrombotic syndrome.<sup>281</sup> A 2020 Cochrane meta-analysis included 28 studies on Rutosides concluding that rutosides probably improve oedema, volume of the leg and pain. Very limited action was demonstrated in ankle perimeter reduction and ulcer healing. Very low evidence support its use for reducing heaviness, cramps, itching, and paraesthesia.<sup>282</sup>

*Analyzed literature possible biases*

Lack of homogenous study populations and blind assessment. Several confounders, including BMI.

*Suggested next research lines*

Properly conducted head-to-head evaluations.

*Related statement in layman's term for public vein-lymphatic awareness*

Rutosides demonstrated to potentially reduce swelling and pain. Some studies suggest it can reduce symptoms after a deep venous thrombosis, but there is no high-quality evidence suggesting its use for post-thrombotic syndrome prevention.

*Suggested pertinent extra readings*

- Pikovskiy O, Rabinovich A. Prevention and treatment of the post-thrombotic Syndrome. Thromb Res 2018;164:116-24.
- Yildiz CE, Conkbayir C, Huseynov E, Sayin OA, Tok O, Kaynak G, et al. The efficiency of O-(beta-hydroxyethyl)-rutosides in reducing the incidence of superficial venous insufficiency in patients with calf muscle pump dysfunction. Phlebology 2017;32:179-84.
- Belczak SQ, Sincos IR, Campos W, Beserra J, Nering G, Aun R. Venotonic drugs for chronic venous disease: A randomized, double-blind, placebo-controlled parallel-design trial. Phlebology 2014;29:454-60.

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## 6. Calcium dobesilate evidence-based use in chronic venous disease management

### Query used for the literature search

(calcium dobesilate) AND ((vein) OR (venous))

### Main findings

Calcium dobesilate (2,5-dihydroxy-benzenesulfonate) is a synthetic drug providing anti-inflammatory, anti-thrombotic and anti-oxidative effects. It reduces capillary hyperpermeability and blood viscosity and it inhibits platelet aggregation. Laboratory data showed an increase in nitric oxide synthase and a decrease in prostaglandin release.<sup>283</sup> Clinically, it demonstrated a potential benefit in the control of edema, swelling, restless leg and pain in CVD patients. Nevertheless, Martinez-Zapata *et al.* showed no significant improvements using calcium dobesilate compared to placebo in CVD related edema, symptoms, or quality of life.<sup>270</sup> A hypothesis has been made by Ciapponi *et al.* on a preferential role of calcium dobesilate in the most advanced stages, but an evidence-based confirmation is still lacking.<sup>284</sup> Cases of transient agranulocytosis were reported following the use of calcium dobesilate, but a recent Cochrane revision did not identify a significant risk of it, showing just gastrointestinal events as possible side effects.<sup>280</sup>

### Analyzed literature possible biases

Heterogenous study populations.

### Suggested next research lines

- Head to head comparison with other venous active drugs.
- Safety studies needed on the wide populations to estimate the risk of agranulocytosis.

### Related statement in layman's term for public vein-lymphatic awareness

Calcium Dobesilate demonstrated to potentially reduce venous incompetence related swelling, edema and pain, but more evidence is needed.

### Suggested pertinent extra readings

a) Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, Stein AT, Moreno RM, Vargas E, *et al.* Phlebotonics for venous insufficiency. *Cochrane Database Syst Rev* 2020;11:CD003229.

b) Rabe E, Ballarini S, Lehr L; Doxium EDX09/01 Study Group. A randomized, double-blind, placebo-controlled, clinical study on the efficacy and safety of calcium

dobesilate in the treatment of chronic venous insufficiency. *Phlebology* 2016;31:264-74.

c) Martinez-Zapata MJ, Moreno RM, Gich I, Urrútia G, Bonfill X; Chronic Venous Insufficiency Study Group. A randomized, double-blind multicentre clinical trial comparing the efficacy of calcium dobesilate with placebo in the treatment of chronic venous disease. *Eur J Vasc Endovasc Surg* 2008;35:358-65.

d) Ciapponi A, Laffaire E, Roqué M. Calcium dobesilate for chronic venous insufficiency: a systematic review. *Angiology* 2004;55:147-54.

## 7. Pentoxifylline evidence-based use in chronic venous disease management

### Query used for the literature search

(pentoxifylline) AND ((vein) OR (venous))

### Main findings

Pentoxifylline is a xanthine derivative drug prescribed for arterial claudication, venous ulceration and sever alcoholic hepatitis. Its actions include reduction of blood viscosity by erythrocyte aggregation and fibrinolysis stimulation. It also demonstrated to improve leukocyte deformability and chemotaxis, while inhibiting neutrophil degranulation and endothelial leukocyte adhesion. Pentoxifylline can lower the production of inflammatory cytokines.<sup>285</sup> A recent meta-analysis identified a total of 13 randomized clinical trials reporting how, compared with placebo, pentoxifylline significantly improved the ulcer healing rate (RR=1.59, 95% CI: 1.22 to 2.07, P<0.001) and the improvement rate (RR=2.36, 95% CI: 1.31 to 4.24, P=0.004). Pentoxifylline also shortened mean duration of complete wound healing (P=0.007) and reduced ulcer size (P=0.02). Among the side effects, it increased the incidence of gastrointestinal disturbances (RR=2.29, 95% CI: 1.04 to 5.03, P=0.04).<sup>286</sup> In another systematic review assessing pentoxifylline outcomes, sulodexide resulted not inferior to pentoxifylline.<sup>273</sup> More evidence is needed to provide high-certainty recommendations. Large-scale, well-designed randomized clinical trials are warranted.

### Analyzed literature possible biases

Not complicated ulcers are usually included in the studies.

### Suggested next research lines

Large-scale, well-designed randomized clinical trials.

### Related statement in layman's term for public vein-lymphatic awareness

Pentoxifylline can be used in venous ulcer management. International guidelines are not univocal in its indication:

the drug use must follow proper evaluation of the expert physician.

#### *Suggested pertinent extra readings*

a) Chaitidis N, Kokkinidis DG, Papadopoulou Z, Hase-maki N, Attaran R, Bakoyiannis C, *et al.* Management of Post-thrombotic Syndrome: A Comprehensive Review. *Curr Pharm Des* 2022;28:550-9.

b) Bonkemeyer Millan S, Gan R, Townsend PE. Venous Ulcers: Diagnosis and Treatment. *Am Fam Physician* 2019;100:298-305.

c) Ahmadi M, Khalili H. Potential benefits of pentoxifylline on wound healing. *Expert Rev Clin Pharmacol* 2016;9:129-42.

d) Pascarella L, Shortell CK. Medical management of venous ulcers. *Semin Vasc Surg* 2015;28:21-8.

### **8. Topical creams evidence-based use in chronic venous disease management**

#### *Query used for the literature search*

(topical) AND (vein)

#### *Main findings*

The market is populated by not properly validated topical products claiming venous and/or lymphatic effects despite the lack of specific evidence-based supporting literature.<sup>287</sup> The analysis of the topical products for wound care is reported in the ulcer section of this document. A 2014 review supported the use of topical maritime pine bark extract for venous insufficiency symptoms, yet in the 2020 Cochrane revision no topical products met the criteria for inclusion in the 2020 Cochrane revision on the topic.<sup>282</sup> Another 2020 Cochrane revision highlighted the absence of validated topicals for the management of superficial venous thrombosis induced inflammation.<sup>218</sup>

#### *Analyzed literature possible biases*

Lack of properly designed studies.

#### *Suggested next research lines*

Randomized comparative trial on homogenous population, assessing objective outcomes.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Topical cream can bring an empirical benefit in venous and/or lymphatic symptoms/signs management, but the scientific literature is lacking strong evidence. An expert physician indication to the right product is mandatory.

#### *Suggested pertinent extra readings*

a) Shaydakov ME, Ting W, Sadek M, Aziz F, Diaz JA, Raffetto JD, *et al.*; American Venous Forum Research Committee. Review of the current evidence for topical treatment for venous leg ulcers. *J Vasc Surg Venous Lymphat Disord* 2022;10:241-7.

b) Woo K, Dowsett C, Costa B, Ebohon S, Woodmansey EJ, Malone M. Efficacy of topical cadexomer iodine treatment in chronic wounds: Systematic review and meta-analysis of comparative clinical trials. *Int Wound J* 2021;18:586-97.

c) O'Meara S, Richardson R, Lipsky BA. Topical and systemic antimicrobial therapy for venous leg ulcers. *JAMA* 2014;25:2534-5.

### **9. Medical honey evidence-based use in chronic venous disease management**

#### *Query used for the literature search*

(honey) AND ((vein) OR (ulcer))

#### *Main findings*

Honey natural medical properties have been considered valuable in wound healing since the Sumerian times, 2000 years before Christ.<sup>288</sup> Honey contains different sugars (fructose, glucose, sucrose and various di and tri-saccharides) and active compounds such as flavonoids, phenolic acid, vitamins, organic acids and enzymes involved in wound healing and anti-oxidant activities. Fibroblasts activity and collagen deposition found to be promoted by honey aminoacids. Its viscosity counteracts the bacteria wound infiltration. Its high sugar content creates an osmotic gradient that stimulates the drainage of the accumulate fluids around the ulcer, while offering an energy source for the cellular components involved in tissue restoration. Moreover, tissue oxygenation is favored by the honey low pH of honey. Honey stimulates the production of hydrogen peroxide resulting in an antimicrobial activity as well as in a release of vascular endothelial growth factor.<sup>289</sup> Honey properties can vary significantly based on the different types of it. Identifying the proper product is therefore mandatory. Defining the standards of the validated medical honey is fundamental in order to avoid use of not properly certified products.<sup>290</sup> Two trials reported a potential benefit in honey use for venous ulcer healing, but a related Cochrane report pointed out the fragility of the data, requesting further investigations before coming to solid recommendation.<sup>291</sup> Making a final conclusion on honey role as topical treatment for improving wound

healing is challenging because of the heterogenous nature of both products and study populations. Honey seems to favor healing in partial thickness burns more quickly than conventional treatment and infected post-operative wounds. Nevertheless, more studies are needed before a recommendation can be made.

*Analyzed literature possible biases*

Different types of honey and heterogenous study populations.

*Suggested next research lines*

- Specific honey types head to head comparison.
- Well designed and conducted RCT trials on VLU healing.

*Related statement in layman's term for public vein-lymphatic awareness*

Specific topicals containing medical honey demonstrated to be useful in partial thickness burns and infected post-operative wounds, while no robust evidence support their use in other type of lesions at the current moment.

*Suggested pertinent extra readings*

- a) Tashkandi H. Honey in wound healing: An updated review. *Open Life Sci* 2021;16:1091-100.
- b) Prasathkumar M, Sadhasivam S. Chitosan/Hyaluronic acid/Alginate and an assorted polymers loaded with honey, plant, and marine compounds for progressive wound healing-Know-how. *Int J Biol Macromol* 2021;186:656-85.
- c) Zhang F, Chen Z, Su F, Zhang T. Comparison of topical honey and povidone iodine-based dressings for wound healing: a systematic review and meta-analysis. *J Wound Care* 2021;30(Sup4):28-36.
- d) Gethin G, Cowman S. Bacteriological changes in sloughy venous leg ulcers treated with manuka honey or hydrogel: an RCT. *J Wound Care* 2008;17:241-7.

**10. Supplement or dietary derived products meaning in chronic venous disease management**

*Query used for the literature search*

("venous insufficiency"[MeSH Terms]) AND (diet OR supplement)

*Main findings*

A recent publication demonstrated the urgency of false claims counteraction related to supplements. More than 80% of the function claims included in the analyzed adver-

tisements are not authorized by the European Food Safety Authority, while more than 20% of disease claims are not allowed by United Europe regulation. More than 70% of analyzed substances are illicit in the case of reduction of disease risk claims.<sup>292</sup> An alarming 2012 publication already pointed out how only 12% of the available products were certified by an independent scientific agency, therefore exposing the consumers to the risk of not properly validated over-the-counter dietary supplements. The issue is of particular concern considering over 50% of the general population has been reported to use these products.<sup>293</sup> Back in 2006 a revision of the literature pointed out the absence of evidence for the benefit of supplements in the prevention of cardiovascular disease.<sup>294</sup> A more recent revision on the general effect of nutrients with antioxidant properties on chronic ulcer healing reported a potential benefit of Omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, and resveratrol along with probiotics. The benefit is more evident in the cases showing an initial deficiency of the related nutrient. Nevertheless, up to the authors knowledge, no solid evidence-based data support a recommendation on the use of dietary supplements in venous disease patients and further properly conducted investigations are needed.<sup>295</sup>

*Analyzed literature possible biases*

- Lack of objective measures in homogeneous study populations.
- In many countries several natural flavonoids are registered under the name of dietary supplements to facilitate the registration process, with no need of the confirmation of their activity and efficacy in proposed doses and administration.

*Suggested next research lines*

- Randomized comparative trials on different supplements use, assessing objective outcomes in homogenous study populations.
- Medical societies discussion with the national and international regulatory institutions for proper validation of venous active drugs and counteraction of not evidenced-based claims for supplements and topicals.

*Related statement in layman's term for public vein-lymphatic awareness*

Up to the knowledge of this experts panel, no supplement or dietary derived has demonstrated to significantly improve venous and or lymphatic function in a significant way.

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*Suggested pertinent extra readings*

a) McDaniel JC. Dietary supplement use by older adults with chronic venous leg ulcers. *Wound Repair Regen* 2020;28:561-72.

b) Kulprachakarn K, Abkom P, Pongtam O, Ounjai-jean S, Thongkham P, Saengyo S, *et al.* Higher Level of Chicken Consumption Associated With Less Severe Venous Disease. *Int J Low Extrem Wounds* 2017;16:251-4.

c) Lees JS, Chapman FA, Witham MD, Jardine AG, Mark PB. Vitamin K status, supplementation and vascular disease: a systematic review and meta-analysis. *Heart* 2019;105:938-45.

d) Cancio A, Eliason MJ, Mercer J, Tran T, Deuster PA, Stephens MB. Third-party certification of dietary supplements: prevalence and concerns. *Mil Med* 2012;177:1460-3.

**11. Dosing and timing of validated venous active drugs treatments**

*Query used for the literature search*

("venous insufficiency/drug therapy"[MeSH Terms]) AND (dose OR duration)

*Main findings*

Validated VAD demonstrated significant efficacy in CVD signs and symptoms management. The different mechanism of action of the different VAD makes a uniformed posology and prescription timing impossible. Yet, even for the same drug, evidence-based indications on dose adjustments, for example based on hemodynamics and/or personal characteristics such as the patient weight, are lacking. At the same time, the duration of the treatment is usually suggested for some months, but without clear specifics, ranging from 1 to 24 months. Preliminary data showed the potential benefit of a dose adjustment of only some drugs. MPFF demonstrated a benefit in doubling the dose in case of pelvic venous disorders. This approach led to a better pain and blood pooling control compared to the single dose approach.<sup>296</sup> MPFF dose-dependent effect was reported already back in 1987, but in an article written in French.<sup>297</sup> In 1993, Sulodexide in increasing dosages was already successfully associated with an improvement of the venous hypertension related symptoms and signs, including leg oedema.<sup>298</sup> No significant benefits were reported in increasing Rutosides dose for CVD treatment.<sup>299</sup> Similarly, in a 2004 review, no significant differences were identified in 1000 mg vs. 1500 mg per day of calcium Dobesilate use for CVD management.<sup>300</sup> Pentoxifylline showed a benefit in some CVD symptoms and in

**8. DRUGS for VENOUS DISEASE**

Leg venous and lymphatic drainage impairment is as common as misinformation on related pills and topicals unfortunately is.

False claims can confer properties to substances not validated by scientific data. Evidence-based content is reported below and at this website: [www.wwinfoundation.com/fake-news-free-project/](http://www.wwinfoundation.com/fake-news-free-project/)

**DRUGS FOR VENOUS DISEASE**

1. An excess of products in the market are claiming activities on the venous-lymphatic system that are not properly scientifically demonstrated. Relying on the available evidence and research as well as expert physicians advice is mandatory.
2. Micronized Purified Flavonoid Fraction (MPFF) demonstrated to be potentially beneficial in all chronic venous disease clinical classes, improving several signs and symptoms.
3. Sulodexide demonstrated to significantly control chronic venous disease signs and symptoms, to favor venous ulcer healing, to reduce the risk of thrombotic recurrence in specific context, to potentially reduce the impact of COVID-induced inflammation.
4. Ruscus aculeatus demonstrated to be potentially beneficial in chronic venous disease related symptoms and edema improvement. More evidence is needed to position it as the most recommended drug.
5. Rutosides demonstrated to potentially reduce swelling and pain. Some studies suggest it can reduce symptoms after a deep venous thrombosis, but there is no high-quality evidence suggesting its use for post-thrombotic syndrome prevention.
6. Calcium Dobesilate demonstrated to potentially reduce venous incompetence related swelling, edema and pain, but more evidence is needed.
7. Pentoxifylline can be used in venous ulcer management. International guidelines are not univocal in its indication: the drug use must follow proper evaluation of the expert physician.
8. Topical cream can bring an empirical benefit in venous and/or lymphatic symptoms/signs management, but the scientific literature is lacking strong evidence. An expert physician indication to the right product is mandatory.
9. Specific topicals containing medical honey demonstrated to be useful in partial thickness burns and infected post-operative wounds, while no robust evidence support their use in other type of lesions at the current moment.
10. Up to the knowledge of this experts panel, no supplement or dietary derived has demonstrated to significantly improve venous and or lymphatic function in a significant way.
11. The duration protocol of the above report substances intake must follow the single case prescription of the expert physician, taking into account the drug registration documents.

Figure 8.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding venous active drugs.

venous wound healing, but with no significant differences between 1000 vs. 1500 mg dosage for ulcer healing.<sup>301</sup> Further adequately powered trials are needed to assess the eventually needed adjustments of dosing and prescription timing of the different venous active drugs (Figure 8).

*Analyzed literature possible biases*

Lack of homogenous outcome measure and heterogenous study populations.

*Suggested next research lines*

Comparison of different dosage and prescription timing regimens.

*Related statement in layman’s term for public vein-lymphatic awareness*

The duration protocol of the above report substances intake must follow the single case prescription of the expert

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physician, taking into account the drug registration documents.

*Suggested pertinent extra readings*

a) Kirienko A, Radak D. Clinical acceptability study of once-daily versus twice-daily micronized purified flavonoid fraction in patients with symptomatic chronic venous disease: a randomized controlled trial. *Int Angiol* 2016;35:399-405.

b) Andreozzi GM, Bignamini AA, Davì G, Palareti G, Matuška J, Holý M, *et al.*; SURVET Study Investigators. Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *Circulation* 2015;132:1891-7.

**9. Graduated compression**

**1. Compression stockings certification requirements**

*Query used for the literature search*

(compression stockings) AND (classification)

*Main findings*

Graduated compression stockings represent a pivotal tool for venous-lymphatic disease management. Their prescription requires appropriate knowledge by the health professional indicating them, as well as by the patient who must understand why proper use and compliance is crucial. The prescribers and users must also be extremely careful in not being victims of the many not certified products claiming effects that have not been demonstrated.<sup>302</sup> Currently, there are several compression hosiery classification systems. The most common one is the RAL-GZG (the German Institute for Quality Assurance and Certification) which is used for certification. The two remaining ones include the CEN (The European Committee for Standardization) classification and the simplified ICC (International Compression Club) classification. In all classifications a pressure range (in mmHg) exerted by the product at the ankle level assessed has been proposed as a more uniform criterion.<sup>303, 304</sup> The medical compression stocking is considered as a medical device, therefore it must demonstrate specific characteristics, including CE mark or FDA approval in the related countries. The FDA considers compression stockings as a class I device exempt from FDA 510k pre-market notification requirements. An official independent certification institute for graduated compression stockings is missing in USA up to

our knowledge (FDA product classification <https://www.accessdata.fda.gov>).

Wherever present, the certification test includes the safety of the used material and the pressure course. Other supplementary tests investigate possible changes in compression behavior during rest phases as well as the wear-out of the product. The certification must assess also the microclimate between the skin and the stocking, as well as the presence of eventual harmful substances and the odor management. The fit of the product is measured to verify the adaptation to the different leg sizes. In case nanomaterials, silver additives, pharmaceutical are used, a higher classification and testing is needed and the product can become class IIa, IIb, III according to the Medical Device Regulation, based also on the associated risk. Increasing awareness on the certification and regulatory aspects is of paramount importance for avoiding ineffective inappropriate products use and to maximize the benefits an appropriate compression demonstrated to bring.

*Analyzed literature possible biases*

Paucity of performance comparisons among the different certification systems.

*Suggested next research lines*

Registry on certified vs. not certified products.

*Related statement in layman's term for public vein-lymphatic awareness*

Compression graduated stocking must be certified, report the exerted pressure in millimetres of mercury and be indicated by an expert health-professional.

*Suggested pertinent extra readings*

a) Office of the Surgeon General (OSG). Confronting Health Misinformation: The U.S. Surgeon General's Advisory on Building a Healthy Information Environment [Internet]. Washington (DC): US Department of Health and Human Services; 2021.

b) Knight Nee Shingler SL, Robertson L, Stewart M. Graduated compression stockings for the initial treatment of varicose veins in people without venous ulceration. *Cochrane Database Syst Rev* 2021;7:CD008819.

c) Dissemmond J, Assenheimer B, Bültemann A, Gerber V, Gretener S, Kohler-von Siebenthal E, *et al.* Compression therapy in patients with venous leg ulcers. *J Dtsch Dermatol Ges* 2016;14:1072-87.

d) Anderson I. Optimising concordance with compression hosiery in the community setting. *Br J Community Nurs* 2015;20:67-72.

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## 2. Compression compliance optimization

### *Query used for the literature search*

(graduated compression) AND (compliance)

### *Main findings*

Graduated compression stockings are a main pillar in lower limb venous and lymphatic disease management, yet the general misconception of their being not easily tolerable by the patient hampers their potential use benefit. The major reasons for lack of patient compliance were identified as related to wrong prescription, including lack of final user education on the topic.<sup>305</sup> According to a recent literature revision, less than two thirds of patients affected by chronic venous disease or deep venous thrombosis are compliant to graduated compression. Lower pressure doses were associated with a better compliance, nevertheless proper data collection on compliance assessment is missing.<sup>306</sup> A 2020 publication on the topic demonstrated four main themes and nine subthemes related to the reasons for non-compliance with graduated compression stockings for lower limb varicose veins. The lack of proper health and non-health professionals education was confirmed as a main justification of the phenomenon. Sociopsychological factors related to the use of graduated compression stockings were also identified.<sup>307</sup> Moreover, training of prescribers was demonstrated to be an important factor in influencing the knowledge, the attitude, and the good practice toward the correct use of graduated elastic compression.<sup>308</sup> The involved prescribers should dedicate time and commitment to educate their patients on the topic, considering that a direct association between the knowledge and the patient attitude was demonstrated as well.<sup>309</sup>

### *Analyzed literature possible biases*

Heterogeneous compliance assessment modalities.

### *Suggested next research lines*

Real world data on compliance measure by homogenous objective parameters.

### *Related statement in layman's term for public vein-lymphatic awareness*

If properly prescribed and applied, compression stockings are highly tolerable. Specific devices can help donning and doffing them.

### *Suggested pertinent extra readings*

a) Knight Nee Shingler SL, Robertson L, Stewart M. Graduated compression stockings for the initial treatment

of varicose veins in people without venous ulceration. *Cochrane Database Syst Rev* 2021;7:CD008819.

b) Jin YH, Wang GH, Sun YR, Li Q, Zhao C, Li G, *et al.* A critical appraisal of the methodology and quality of evidence of systematic reviews and meta-analyses of traditional Chinese medical nursing interventions: a systematic review of reviews. *BMJ Open* 2016;6:e011514.

c) Wade R, Paton F, Woolacott N. Systematic review of patient preference and adherence to the correct use of graduated compression stockings to prevent deep vein thrombosis in surgical patients. *J Adv Nurs* 2017;73:336-48.

d) Craigie S, Tsui JF, Agarwal A, Sandset PM, Guyatt GH, Tikkinen KA. Adherence to mechanical thromboprophylaxis after surgery: A systematic review and meta-analysis. *Thromb Res* 2015;136:723-6.

## 3. Compression prescription education requirements

### *Query used for the literature search*

(graduated compression) AND (prescription)

### *Main findings*

Better and repeated recommendations by the practitioner result in an increase in compliance by 33% of patients.<sup>309</sup> Nevertheless, it is not clear what professional figure is allowed to prescribe medical stockings, if any.<sup>310</sup> Despite the risk/benefit ratio in graduated compression stockings use is greatly in favor of the benefit, side effects could be triggered in case of wrong indication. Scientific societies and institutions should clarify the requirements for both prescription and prescribers eventual educational background.

### *Analyzed literature possible biases*

Lack of clarity on national and international certification and regulatory requirements for graduated compression stockings prescription.

### *Suggested next research lines*

Certification and regulatory evaluation on prescription needs for medical graduated compression stockings.

### *Related statement in layman's term for public vein-lymphatic awareness*

An expert health professional must educate the user of graduated compression stocking on why should them use it and how to use them at best.

### *Suggested pertinent extra readings*

a) Bar L, Brandis S, Marks D. Improving Adherence to Wearing Compression Stockings for Chronic Venous

Insufficiency and Venous Leg Ulcers: A Scoping Review. Patient Prefer Adherence. 2021;15:2085-102.

b) Dawson AJ, Akaberi A, Galanaud JP, Morrison DR, Kahn SR, *et al.*; SOX Trial investigators. Patient-reported reasons for and predictors of noncompliance with compression stockings in a randomized trial of stockings to prevent postthrombotic syndrome. Res Pract Thromb Haemost 2019;4:269-77.

c) Bouman AC, Ten Cate-Hoek AJ, Dirksen CD, Joore MA. Eliciting patients' preferences for elastic compression stocking therapy after deep vein thrombosis: potential for improving compliance. J Thromb Haemost 2016;14:510-7.

d) Sippel K, Seifert B, Hafner J. Donning devices (foot slips and frames) enable elderly people with severe chronic venous insufficiency to put on compression stockings. Eur J Vasc Endovasc Surg 2015;49:221-9.

#### 4. Compression in healthy subjects

*Query used for the literature search*

(graduated compression) AND (healthy)

##### *Main findings*

Healthy subjects at risk of developing swelling are candidate to graduated compression stockings use. Long standing up workers, pregnant women, long haul travelers are examples of this category.<sup>311</sup> An investigation on healthy subjects during 3 hours sitting time demonstrated graduated compression stockings benefit for subjective comfort and increased parasympathetic nerve activity.<sup>312</sup> Healthy healthcare workers were assessed while standing, sitting and walking in a standardized way for 30 minutes, reporting a benefit in graduated compression use for edema control.<sup>313</sup> This finding is in line with the reported oxidative stress reduction in standing up workers wearing compression.<sup>314</sup> Moreover, intermittent walking wearing compression demonstrated to be associated with edema control and perceived exertion reduction in case of graduated compression stocking use.<sup>315</sup> Healthy travelers wearing graduated compression showed edema control, without significant differences in pain and discomfort.<sup>316</sup> A recent randomized comparative trial demonstrated how appropriate compression can be beneficial in edema control and subjective perception during pregnancy.<sup>317</sup> More homogeneous data collections are needed on the topic, particularly regarding the standardization of the physical activity in which the stocking use is measured, always reporting the real inter-face pressure measurement.

##### *Analyzed literature possible biases*

Heterogeneous data collection in standardized muscle mass activation.

##### *Suggested next research lines*

Different compression regimens effect on homogeneous healthy subjects study populations.

##### *Related statement in layman's term for public vein-lymphatic awareness*

Specific certified compression stockings demonstrated to be useful for swelling and subjective comfort control also in healthy subjects subjected to more than 30 minutes standing up or sitting conditions and to pregnancy.

##### *Suggested pertinent extra readings*

a) Négyesi J, Hortobágyi T, Hill J, Granacher U, Nagatomi R. Can Compression Garments Reduce the Deleterious Effects of Physical Exercise on Muscle Strength? A Systematic Review and Meta-Analyses. Sports Med 2022;52:2159-75.

b) Mota GR, Simim MA, Dos Santos IA, Sasaki JE, Marocolo M. Effects of Wearing Compression Stockings on Exercise Performance and Associated Indicators: A Systematic Review. Open Access J Sports Med 2020;11:29-42.

#### 5. Compression indications and specifics through the CEAP C1-C6 spectrum

*Query used for the literature search*

(graduated compression) AND (venous)

##### *Main findings*

Graduated compression stockings use has been suggested in all CEAP clinical classes with different grades of recommendation in the different guidelines.<sup>7</sup> A recent Cochrane reported insufficient high-certainty evidence to determine if compression stockings are effective as the sole initial treatment of chronic venous disease and if there is superiority of any product.<sup>318</sup> Compression stockings are effective in venous ulcer healing and recurrence reduction, as well as in decreasing lipodermatosclerosis induration.<sup>319</sup> A pressure dose increase is usually recommended for the most advanced disease stages, yet solid evidence on this practice is still missing.<sup>120</sup> The role of compression in preventing venous disease evolution is still debatable, with only limited data in its support.<sup>320</sup> Considering a significant number of graduated compression stocking inappropriate fitting have been reported, proper education



of healthcare professionals and public is of paramount importance.

*Analyzed literature possible biases*

Lack of interface pressure measurement.

*Suggested next research lines*

- Compression best dose and type in the different venous-lymphatic disease stages.
- Impact on health-related quality of life and cost-effectiveness.

*Related statement in layman's term for public vein-lymphatic awareness*

Specific certified compression stockings demonstrated to be beneficial in all the stages of leg venous disease, in venous ulcer recurrence reduction, in lymphatic disorders, in thrombo-embolism and post-thrombotic prevention and management.

*Suggested pertinent extra readings*

a) da Silva LF, Porto MS, de Sousa AB, Avena KM. Graduated compression stockings as a prophylactic measure in venous thromboembolism and edema of lower limbs triggered by air travel: a systematic review of clinical trials. *J Vasc Bras* 2021;20:e20200164.

b) Mościcka P, Szewczyk MT, Cwajda-Białasik J, Jawień A. The role of compression therapy in the treatment of venous leg ulcers. *Adv Clin Exp Med* 2019;28:847-52.

c) Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, *et al.* Indications for medical compression stockings in venous and lymphatic disorders: An evidence-based consensus statement. *Phlebology* 2018;33:163-84.

d) de Carvalho MR, de Andrade IS, de Abreu AM, Leite Ribeiro AP, Peixoto BU, de Oliveira BG. All about compression: A literature review. *J Vasc Nurs* 2016;34:47-53.

**6. Superficial and deep venous post-procedural compression timing and dosing**

*Query used for the literature search*

(compression) AND (post-procedural)

*Main findings*

Graduated compression following vein procedures is recommended in a heterogeneous way in the different international guidelines, with pressure ranging from 16 to 40 mmHg and a timing ranging from 24 hours to 3 weeks.<sup>7</sup> A recent review on graduated compression peri-procedural

use in low-risk surgical patients pointed out the need of properly powered studies before delivering high grade recommendations.<sup>321</sup> Another review demonstrated the heterogeneity in the outcome measures used in this topic investigations, therefore suggesting larger data collection on specific assessments of not only thrombotic incidence, rather pain and quality of life that demonstrated a potential benefit in compression use.<sup>322</sup> Indeed, the most recent review on the topic reported a better pain control and a faster return to normal activities following the use of post-procedural compression, yet with the confirmed need of larger high-quality studies on the topic.<sup>323</sup> A randomized comparative trial demonstrated a better pain control by the compression group, particularly in case of concomitant phlebectomies, but with no significant difference in quality of life and return to normal activities. It should be noted that both study groups wore compression bandages, introducing a potential bias in the compression analysis.<sup>122</sup> Considering the potential benefits of post-procedural compression and the low associated risk, further studies should be dedicated on the topic, including the currently lacking area of deep venous post-procedural management.

*Analyzed literature possible biases*

Different outcome measures in heterogeneous procedures and lack of interface pressure measurement.

*Suggested next research lines*

- Multicenter RCT on homogeneous outcome measures.
- Registry data.

*Related statement in layman's term for public vein-lymphatic awareness*

- Certified compression stockings can be useful after a procedure on the venous system.
- Only expert health-professionals can recommend specific compression type and duration.

*Suggested pertinent extra readings*

a) Tan MKH, Salim S, Onida S, Davies AH. Postsclerotherapy compression: A systematic review. *J Vasc Surg Venous Lymphat Disord* 2021;9:264-74.

b) Chou JH, Chen SY, Chen YT, Hsieh CH, Huang TW, Tam KW. Optimal duration of compression stocking therapy following endovenous thermal ablation for great saphenous vein insufficiency: A meta-analysis. *Int J Surg* 2019;65:113-9.

c) Lurie F, Lal BK, Antignani PL, Blebea J, Bush R, Caprini J, *et al.* Compression therapy after invasive treat-

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ment 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.

d) Wade R, Paton F, Woolcott N. Systematic review of patient preference and adherence to the correct use of graduated compression stockings to prevent deep vein thrombosis in surgical patients. *J Adv Nurs* 2017;73:336-48.

## 7. Bandages indication in venous and lymphatic disease management

### Query used for the literature search

(bandage) AND ((venous) OR (lymphatic))

### Main findings

Up to our knowledge, international guidelines are not indicating superiority of bandaging over graduated compression stockings in venous ulcer or lymphedema setting. No superiority of a bandaging technique over another has been reported either, apart multicomponent vs. single component in venous ulcer treatment.<sup>7</sup> A recent Cochrane review highlighted the importance of compression in venous ulcer healing, reporting a faster and wider resolution, with potential benefits also in pain control and disease specific quality of life. Yet, not enough data have been identified to conclude on the superiority of a specific compression type, both in terms of clinical and cost-effectiveness aspects.<sup>246</sup> Compression is the pillar also of lymphedema management, yet proper knowledge of the available literature leads to consider not only the pressure but also the applied stiffness.<sup>324</sup> Not recent literature pointed out the possible advantages of an initial phase of bandage use followed by stockings application, but more solid data are needed before delivering high grade recommendations on this compression strategy.<sup>325</sup> Training in bandaging is of paramount importance to guarantee proper clinical effects as well as homogenous scientific data collection: a significant interface pressure variability can be caused by inappropriate bandaging technique.<sup>326</sup>

### Analyzed literature possible biases

Lacking of Interface pressure measurement.

### Suggested next research lines

Head-to-head comparison between stockings and bandages in homogenous study populations.

### Related statement in layman's term for public vein-lymphatic awareness

Bandages with different features can be helpful in customizing a compression therapy on the specific need of the venous-lymphatic patient. Only expert professionals can apply bandages properly and at the desired pressure level.

### Suggested pertinent extra readings

a) Rezende GC, O'Flynn B, O'Mahony C. Smart Compression Therapy Devices for Treatment of Venous Leg Ulcers: A Review. *Adv Healthc Mater* 2022;22:e2200710.

b) Tai HQ, Chaen LC, Boey J, Kime S, Rial R, Montero EC, *et al.* A dual pressure indicator, two-layer compression system for treatment of venous leg ulcers: a review. *J Wound Care* 2021;30(Sup12):S6-S12.

c) Cardoso LV, De Fátima Guerreiro Godoy M, Czorny RC, De Godoy JM. Using bioelectrical impedance analysis to compare the treatment of edema with the Unna's boot and noncompression in individuals with venous ulcers. *J Vasc Nurs* 2019;37:58-63.

d) Chang DW, Masia J, Garza R 3rd, Skoracki R, Nelligan PC. Lymphedema: Surgical and Medical Therapy. *Plast Reconstr Surg* 2016;138(3 Suppl):209S-18S.

## 8. Adjustable compression role indication in venous and lymphatic disease management

### Query used for the literature search

adjustable compression wrap

### Main findings

A 2019 review analyzed 16 papers on adjustable compression wraps use for venous ulcer healing. The results demonstrated the related improvement in healing time and quality of life, with a potential significant cost-efficacy.<sup>327</sup> Another more recent investigation confirmed the cost-effectiveness of adjustable compression wraps compared to inelastic bandage, moreover providing a better interface pressure maintenance.<sup>248</sup> Adjustable compression wraps demonstrated superiority against inelastic bandages also in chronic venous edema reduction, moreover at an interface pressure of 40 mmHg vs. 60 mmHg applied by bandaging, including in the analysis the initial decongestive treatment phase.<sup>328</sup> A 2021 randomized comparative trial investigated the efficacy of conventional multilayer short-stretch bandaging, and a velcro adjustable compression wrap in lower limb lymphedema patients. The outcomes showed significant improvements in lower limb volume and subcutaneous thickness, as well as in appearance, symptoms and quality of life scores,

therefore positioning the adjustable compression wrap as a valid alternative to bandaging in the active phase of lymphedema treatment.<sup>329</sup> It should be noted further studies are needed before delivering high grade recommendations on the topic and that only a specific brand of adjustable compression brand has been involved in the above mentioned studies, for which the results can not be generalized until other products will be tested in an evidence based manner.

*Analyzed literature possible biases*

Only one brand used in the reported scientific studies.

*Suggested next research lines*

RCT involving different adjustable compression wraps.

*Related statement in layman's term for public vein-lymphatic awareness*

A specific adjustable compression wrap demonstrated clinical and cost effectiveness superiority in ulcer healing and leg venous-lymphatic edema compared to bandaging.

*Suggested pertinent extra readings*

a) Balcombe L, Miller C, McGuinness W. Approaches to the application and removal of compression therapy: A literature review. *Br J Community Nurs* 2017;22(Sup10):S6-14.

b) Palacios FS, Rathbun SW. Medical Treatment for Postthrombotic Syndrome. *Semin Intervent Radiol* 2017;34:61-7.

c) Williams A. A review of the evidence for adjustable compression wrap devices. *J Wound Care* 2016;25:242-7.

**9. Intermittent pneumatic compression indication in venous-lymphatic disease management**

*Query used for the literature search*

intermittent pneumatic compression

*Main findings*

Intermittent pneumatic compression use for venous ulcer or thromboprophylaxis or lymphedema management is recommended in a heterogeneous way in the different international guidelines with a lack of standardization in the dosage and timing of the related protocols.<sup>7</sup> A recent randomized comparative trial results suggests intermittent pneumatic compression can be a valuable adjunct to wound healing standard compression treatment, particularly in case of large or painful venous-lymphatic ulcers.<sup>330</sup> Nevertheless, significant data sup-

porting the use of intermittent pneumatic compression alone without other forms of compression are still lacking.<sup>250</sup> In the thromboprophylaxis context, evidence suggests that adding intermittent pneumatic compression to pharmacological prophylaxis can reduce the incidence of thrombo-embolism, but with a low-certainty evidence.<sup>331</sup> A review conducted on lymphedema patients reported low-level evidence showing the benefit of 45-60 minutes at 30-60 mmHg application, yet highlighting the need of proper protocols validations.<sup>332</sup> The controversial topic of intermittent pneumatic compression use in lymphedema was reported also in a recent consensus document highlighting agreement for the adjuvant therapy in the maintenance phase of treatment, but less so in its initial phases.<sup>333</sup>

*Analyzed literature possible biases*

Lack of protocol standardization and interface pressure measurement.

*Suggested next research lines*

Different protocols comparison in homogeneous study populations.

*Related statement in layman's term for public vein-lymphatic awareness*

Intermittent pneumatic compression represents a valuable option in leg venous ulcer, thrombo-embolism prophylaxis and edema management. The timing and dosage is variable and must be indicated by the expert health-professional based on the single specific case.

*Suggested pertinent extra readings*

a) Bobrek K, Nabavizadeh R, Nabavizadeh B, Master V. How to Care and Minimize the Sequelae of Lower Extremity Lymphedema. *Semin Oncol Nurs* 2022;38:151270.

b) Kakkos S, Kirkilesis G, Caprini JA, Nicolaidis AN, Stansby G, Reddy DJ, *et al.* Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism. *Cochrane Database Syst Rev* 2022;1:CD005258.

c) Lobastov K, Sautina E, Alencheva E, Bargandzhiya A, Schastlivtsev I, Barinov V, *et al.* Intermittent Pneumatic Compression in Addition to Standard Prophylaxis of Postoperative Venous Thromboembolism in Extremely High-risk Patients (IPC SUPER): A Randomized Controlled Trial. *Ann Surg* 2021;274:63-9.

d) Aleksandrowicz H, Owczarczyk-Saczonek A, Placek W. Venous Leg Ulcers: Advanced Therapies and New Technologies. *Biomedicines* 2021;9:1569.

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## 10. Graduated compression safety profile and contra-indications

*Query used for the literature search*

(graduated compression) AND (side effects)

### Main findings

Graduated compression stockings demonstrated to be a main pillar in venous and lymphatic disease management, moreover with a high safety profile. Possible contraindications include severe congestive cardiac failure (NYHA IV). However, reducing moderate oedemas, without shifting larger blood volumes towards the right heart, can be beneficial and achievable by using light medical compression stocking.<sup>334</sup> In a similar way, peripheral arterial disease represents a possible contraindication in its most severe forms, yet, in specifically selected patients, specifically designed compression stockings showed no reduction in microperfusion and an improvement in the perfusion

of definite limb locations.<sup>335</sup> There are other local conditions in which stockings may cause damage, among which advanced peripheral neuropathy, fragile tissue paper skin over the bony prominences, severe limb asymmetry, dermatitis and allergic reactions to the fabric.<sup>311</sup> This observation highlights the importance of proper health professional and patients education in compression prescription and use, in order to maximize its benefits, reducing its already minimal risks. In the same way, proper interaction among international experts dedicated to the topic is needed to agree not only on the absolute contraindications, but also on the relative ones, that currently remain quite heterogeneous in the different guidelines (Figure 9).<sup>336</sup>

### Analyzed literature possible biases

Lack of registry data.

### Suggested next research lines

Real world data.

### Related statement in layman's term for public vein-lymphatic awareness

Properly prescribed compression is safe. Possible contraindications are: neuropathy, skin alterations, heart failure, severe limb asymmetry. In peripheral arterial disease compression can be of benefit in specific cases, after careful evaluation.

### Suggested pertinent extra readings

a) Knight Nee Shingler SL, Robertson L, Stewart M. Graduated compression stockings for the initial treatment of varicose veins in people without venous ulceration. *Cochrane Database Syst Rev* 2021;7:CD008819.

b) Stücker M, Danneil O, Dörler M, Hoffmann M, Kröger E, Reich-Schupke S. Safety of a compression stocking for patients with chronic venous insufficiency (CVI) and peripheral artery disease (PAD). *J Dtsch Dermatol Ges* 2020;18:207-13.

c) Franks P, Barker J, Collier M, Gethin G, Haesler E, Jawien A, *et al.* Management of patients with venous leg ulcer: challenges and current best practice. *J Wound Care* 2016;6:1-67.

## 10. Lymphedema-lipedema

### 1. Lymphedema pathophysiology

*Query used for the literature search*

((lymphedema[MeSH Terms]) AND ((pathophysiology [MeSH Terms])) OR (causes[MeSH Terms]))

## 9. COMPRESSION

Venous and lymphatic return from the leg toward the heart has to overcome the force of gravity. Proper certified compression tools demonstrated to be of potential great help.

Evidence-based statements are reported below and at this website: [www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)



### COMPRESSION

1. Compression graduated stocking must be certified, report the exerted pressure in millimeters of mercury and be indicated by an expert health-professional.
2. If properly prescribed and applied, compression stockings are highly tolerable. Specific devices can help donning and doffing them.
3. An expert health professional must educate the user of graduated compression stocking on why should them use it and how to use them at best.
4. Specific certified compression stockings demonstrated to be useful for swelling and subjective comfort control also in healthy subjects subjected to more than 30 minutes standing up or sitting conditions and to pregnancy.
5. Specific certified compression stockings demonstrated to be beneficial in all the stages of leg venous disease, in venous ulcer recurrence reduction, in lymphatic disorders, in thrombo-embolism and post-thrombotic prevention and management.
6. Certified compression stockings can be useful after a procedure on the venous system. Only expert health-professionals can recommend specific compression type and duration.
7. Bandages with different features can be helpful in customizing a compression therapy on the specific need of the venous-lymphatic patient. Only expert professionals can apply bandages properly and at the desired pressure level.
8. A specific adjustable compression wrap demonstrated clinical and cost effectiveness superiority in ulcer healing and leg venous-lymphatic edema compared to bandaging.
9. Intermittent pneumatic compression represents a valuable option in leg venous ulcer, thrombo-embolism prophylaxis and edema management. The timing and dosage is variable and must be indicated by the expert health-professional based on the single specific case.
10. Properly prescribed compression is safe. Possible contraindications are: neuropathy, skin alterations, heart failure, severe limb asymmetry. In peripheral arterial disease compression can be of benefit in specific cases, after careful evaluation.

Figure 9.—Public vein-lymphatic awareness evidence-based statements in layman's terms regarding graduated compression.

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((lipedema[MeSH Terms]) AND ((pathophysiology [MeSH Terms]) OR (causes[MeSH Terms]))

### Main findings

Lymphedema is defined as an insufficiency in lymph drainage, due to vessel dysfunction and/or to an impairment in fluid generation, transport and outflow. It is characterized by a progressive accumulation of liquids in the interstitium. Differently from what still too often believed, the liquid is not always protein-rich.<sup>337</sup> Lymphedema can be “primary” if mainly associated with a genetic background, or “secondary” if caused by a specific etiology compromising the lymphatic function (tissue damage, vessel obstruction or lymph nodes compromise).<sup>338</sup> Trauma, including surgery and lymphatic tissue dissection, infections and radiations are among the most common causes of secondary lymphedema. Lymphedema can be also the consequence of cardiac pump or renal failure.<sup>339</sup> A tight interconnection exists between veins and lymphatics functions, the two of them compensating each other, until an overload point in which the insufficiency of one can destabilize the other. Such condition is known as “phlebo-lymphedema.”<sup>17</sup> Experts in the field are currently debating on the correlations between lymphedema and the so called “lipedema,” discussing even the same nomenclature. This fat tissue alteration is characterized by symmetrical, disproportional distribution of fat deposited in the lower limbs and/or upper limbs of only women. Capillaries fragility in lipedema is testified by a tendency toward ecchymosis. Vein and lymphatics can be involved along the progression of the disease, configuring a mixed patho-physiology. While the lipedema pathophysiology details remain uncertain, a genetic component has been identified in up to 60% of cases. Fat hyperplasia and hypertrophy has been demonstrated, together with a tissue hypoxia that could explain the associated inflammatory state of these patients. Nevertheless, histopathology of lipedema remains not pathognomonic and further studies are encouraged.<sup>340</sup> Lymphedema, phlebo-lymphedema and lipedema are too often underdiagnosed and poorly treated conditions, leading to chronic psycho-physical impairment, requiring expert management. Further research is needed to define the patho-physiology aspects and intersections involved in lymphedema and lipedema development.

### Analyzed literature possible biases

Possible mixture of venous, lymphatic and fat components in the pathophysiology investigations.

### Suggested next research lines

- Pure lipedema study models without lymphatic involvement.
- Pure venous study models without lymphatic involvement.

### Related statement in layman's term for public vein-lymphatic awareness

Lymphedema is a chronic fluids accumulation. Lipedema is an inflammation of the leg fat tissue, possibly associated with lymphedema.

### Suggested pertinent extra readings

- a) Westcott GP, Rosen ED. Crosstalk Between Adipose and Lymphatics in Health and Disease. *Endocrinology* 2022;163:bqab224.
- b) Katzer K, Hill JL, McIver KB, Foster MT. Lipedema and the Potential Role of Estrogen in Excessive Adipose Tissue Accumulation. *Int J Mol Sci* 2021;22:11720.
- c) Kruppa P, Georgiou I, Biermann N, Prantl L, Klein-Weigel P, Ghods M. Lipedema-Pathogenesis, Diagnosis, and Treatment Options. *Dtsch Arztebl Int* 2020;117:396-403.
- d) Jiang X, Nicolls MR, Tian W, Rockson SG. Lymphatic Dysfunction, Leukotrienes, and Lymphedema. *Annu Rev Physiol* 2018;80:49-70.

## 2. Lymphedema classification and staging

### Query used for the literature search

(lymphedema) AND (classification) OR (staging)

### Main findings

Different classification and staging systems are available for lymphedema, but there is not a globally recognized single method providing a comprehensive description of the condition.<sup>7, 341</sup> Moreover, the used terminology can be confounding as not universally adopted.<sup>342</sup>

The International Society of Lymphology recognizes a 4 stages system:

- 0) LATENT lymphedema: swelling is not yet evident despite initial alterations in drainage and related symptoms. It can be transitory and persists years before it manifests itself clinically;
- 1) REVERSIBLE EDEMA: accumulation of fluid of high protein content reverted by limb elevation. The edema becomes pitting;
- 2) Not-REVERSIBLE EDEMA: involution toward fibrotic tissue with edema that is not usually resolved by

limb elevation. Pitting is evident but can disappear in case of advanced fibrotic involution;

3) ELEFANTIASIS: massive lymphatic compromise and fibrosis, associated with skin changes such as acanthosis.

A single person can present multiple stages at the same time, based on the different involvement of the lower limb parts. As reported by the same International Society of Lymphology, this staging refers just to the physical appearance of the disease, not contemplating the pathogenetic mechanism, the genetic vs. environmental compromise grade. An attempt to quantify the severity has been made also by proposing to use the limb volume excess compared to the contralateral limb:

- mild (>5%, <20%);
- moderate (>20%, <40%);
- severe (>40%).

There is not real agreement on these values, as other groups consider “minimal” a variation in between 5% and 10%, while in between 10% and 20% is considered “mild”.<sup>343</sup> This staging system is biased by multiple factors influencing the same limb volume (vascular and musculoskeletal) and by the contralateral limb possible lymphatic compromise. A classification advancement should take into consideration also possible complications (skin infections or ulceration) and quantify the impact of the disease on the patient quality of life.

#### Analyzed literature possible biases

Lack of staging system intra and interobserver validation studies.

#### Suggested next research lines

Validation of a homogeneous globally recognized lymphedema classification system, including a severity scale and quality of life measures.

#### Related statement in layman's term for public vein-lymphatic awareness

Lymphedema is a progressive disease whose stage must be precisely identified by an expert.

#### Suggested pertinent extra readings

a) Lee E, Biko DM, Sherk W, Masch WR, Ladin-Torres M, Agarwal PP. Understanding Lymphatic Anatomy and Abnormalities at Imaging. *Radiographics* 2022;42:487-505.

b) Cirocchi R, Amabile MI, De Luca A, Frusone F, Tripodì D, Gentile P, *et al.* New classifications of axillary

lymph nodes and their anatomical-clinical correlations in breast surgery. *World J Surg Oncol* 2021;19:93.

c) Gordon K, Varney R, Keeley V, Riches K, Jeffery S, Van Zanten M, *et al.* Update and audit of the St George's classification algorithm of primary lymphatic anomalies: a clinical and molecular approach to diagnosis. *J Med Genet* 2020;57:653-9.

### 3. Lymphedema signs, symptoms and diagnostic work-up

#### Query used for the literature search

(lymphedema[MeSH Terms]) AND ((signs[MeSH Terms]) OR (symptoms[MeSH Terms]))

#### Main findings

Lymphedema diagnosis starts from a careful assessment of the patient history, signs and symptoms. Family predisposition, previous trauma, inflammatory or infective conditions affecting the lymphatic system must be promptly reported. Chronic swelling, skin infections and progressive trophic changes suggest the diagnosis.<sup>344</sup> The Kaposi-Stemmer sign (impossibility to pinch the skin on the foot or hand) has a good sensitivity for lymphedema prediction. Yet, its specificity is moderate, therefore instrumental diagnostic is recommended to make an objective diagnosis.<sup>345</sup> The limb volume can be measured by tape, water displacement (gold-standard) or perometry. The fibrosis degree can be assessed by a tonometer, while bioimpedance can detect the tissue texture. Ultrasound scanning can detect the fluid and fibrotic components both at the dermal and subdermal levels, in a simple and cost-effective modality. Ultrasound elastography represents a valuable improvement in moderate-to-advanced lymphedema stages characterization.<sup>83</sup> Lymphoscintigraphy remains a fundamental diagnostic tool in lymphatic drainage evaluation, yet associated with radiation exposure.<sup>343</sup> CT and MRI are indicated for high imaging sensitivity and specificity. Moreover, CT offers the advantage of identifying also possible causes of secondary lymphedema, while MRI lymphangiography provides details of the lymphatic system. The detailed function of the lymphangions can be depicted by Near Infra-Red Fluorescence using indocyanine green, which is limited in its tissue penetration depth though.<sup>346</sup> A careful evaluation of clinical and instrumental data by an expert lymphologist is then needed for a proper diagnostic work-up.

#### Analyzed literature possible biases

Lack of signs and symptoms objective quantification tools.

### *Suggested next research lines*

Diagnostic options cost-effectiveness analysis.

### *Related statement in layman's term for public vein-lymphatic awareness*

Lymphedema can manifest as swelling, redness, skin infections, abnormal tissue proliferation. At least ultrasound scanning must be performed, eventually together with more advanced techniques based on the specific case.

### *Suggested pertinent extra readings*

a) Lee E, Biko DM, Sherk W, Masch WR, Ladinno-Torres M, Agarwal PP. Understanding Lymphatic Anatomy and Abnormalities at Imaging. *Radiographics* 2022;42:487-505.

b) Goss JA, Greene AK. Sensitivity and Specificity of the Stemmer Sign for Lymphedema: A Clinical Lymphoscintigraphic Study. *Plast Reconstr Surg Glob Open* 2019;7:e2295.

c) Keo HH, Gretener SB, Staub D. Clinical and diagnostic aspects of lymphedema. *Vasa* 2017;46:255-61.

## **4. Lymphedema treatment protocol**

### *Query used for the literature search*

(lymphedema[MeSH Terms]) AND (treatment[MeSH Terms])

### *Main findings*

A recent review pointed out the lack of solid guidelines in lymphedema management, due to the lack of properly conducted studies.<sup>79</sup> Enhanced self-care protocols, including self-massage, deep breathing, proper hygiene, weight management, exercise and graduated compression demonstrated their pivotal importance in both primary and secondary lymphedema.<sup>347</sup> Nevertheless, proper standardization is needed to make the outcome reproducible and therefore evidence-based. A typical example can be found in the Complex Decongestive Physiotherapy, whose quality is empirically globally recognized, but whose lack of standardization hampers strong recommendations in its support, particularly concerning the manual drainage.<sup>348</sup> A fundamental concept is the chronic nature of the disease, for which patient education on awareness, self-management and compliance is mandatory. Based on the limb volume variation and the edema fluidity switch toward fibrosis, different compression and follow-up protocols have to be applied. The involvement of an interdisciplinary working group must include the physi-

cian specialized in lymphatic treatment, properly nursing staff, nutrition and exercise experts. The psychological component must not be underestimated, for which proper consulting is not to be forgotten. Objective evaluation of the lower limb lymphedema impact on quality of life is feasible by the dedicated LymphQOL questionnaire. Immediate surgical approach is universally discouraged as first line treatment and, whenever indicated, is not considered definitive for the resolution of the chronic lymphedema condition, which requires a permanent life-style adaptation.<sup>349</sup>

### *Analyzed literature possible biases*

Lack of standardization in complex decongestive therapy report.

### *Suggested next research lines*

Publication of a globally recognized lymphedema management protocol best on grading system or at least on best practice.

### *Related statement in layman's term for public vein-lymphatic awareness*

Lymphedema management includes conservative multi-specialty expert assessment, validated protocols of patients education, skin hygiene, compression, mechanical lymphatic drainage, specific physical exercises. Mesotherapy is not a validated option. No drug has been currently validated to increase lymphatic drainage, including diuretics.

### *Suggested pertinent extra readings*

a) Walker J, Tanna S, Roake J, Lyons O. A systematic review of pharmacologic and cell-based therapies for treatment of lymphedema (2010-2021). *J Vasc Surg Venous Lymphat Disord* 2022;10:966-975.e1.

b) Lafuente H, Jaunarena I, Ansuategui E, Lekuona A, Izeta A. Cell therapy as a treatment of secondary lymphedema: a systematic review and meta-analysis. *Stem Cell Res Ther* 2021;12:578.

c) Russo S, Walker JL, Carlson JW, Carter J, Ward LC, Covens A, *et al.* Standardization of lower extremity quantitative lymphedema measurements and associated patient-reported outcomes in gynecologic cancers. *Gynecol Oncol* 2021;160:625-32.

d) Ramachandran S, Chew KY, Tan BK, Kuo YR. Current operative management and therapeutic algorithm of lymphedema in the lower extremities. *Asian J Surg* 2021;44:46-53.

## 5. Lymphedema surgical indications and technical options

### Query used for the literature search

(lymphedema[MeSH Terms]) AND (treatment[MeSH Terms])

### Main findings

Modern lymphatic management offers valuable surgical options for lymphedema, including lymphaticovenular anastomosis and vascularized lymph node transfer. While lymphatic-vein anastomosis is aimed to re-directed the lymphatic drainage into the venous system, vascularized lymph node transfer replaces the damaged or excised lymph nodes, favoring lymph absorption and lymphoangiogenesis. A significant improvement in quality of life has been demonstrated following both lymphatic-vein anastomosis and vascularized lymph node transfer, regardless of lymphedema etiology, stage, or time since diagnosis. Further research is needed to include both objective measurements in the comparison of the two techniques.<sup>338, 350</sup> Differently from vascularized lymph node transfer, lymphatic vein anastomosis is usually reserved to less severe lymphedema stages, therefore making a proper randomized comparative analysis currently not feasible because of the patient selection bias. Another major issue in the comparison is the lymphatic-vein anastomosis patency in the medium-long term. Indeed, more than 50% of lymphatic-vein anastomosis have been reported to be occluded at 12 months: a finding suggesting the importance of referring the patient only to highly specialized centers. Both vascularized lymph node transfer and lymphatic vein anastomosis present also technical matters of debate. While the vascularized lymph node transfer optimal recipient site location is still debated, the number of needed lymphatic-vein anastomosis remains an object of discussion.<sup>351</sup> Apart the procedures aimed to restore a lymphatic drainage, lymphedema can lead to an indication also to reductive surgical techniques such as direct excision, suction assisted protein lipectomy or radical reduction with perforator preservation. Reductive procedures are indicated in the most advanced stages of the disease. As per the lymphatic-vein anastomosis and vascularized lymph node transfer, only highly specialized centers should perform reductive surgery as this demonstrated to lead to potentially satisfactory results, but not without a significant risk of complications such as infection, lymphatic fistulas, wound breakdown, hyperkeratosis, ulceration, and the aggravation of the same lymphedema.<sup>352</sup>

### Analyzed literature possible biases

Lack of properly designed randomized comparative trials on the different surgical techniques.

### Suggested next research lines

Properly conducted randomized investigations on proper indication and timing to lymphatic surgery.

### Related statement in layman's term for public vein-lymphatic awareness

Lymphedema surgical treatment must be performed only in highly experienced centers and once the conservative approach have demonstrated to be insufficient.

### Suggested pertinent extra readings

a) Fallahian F, Tadisina KK, Xu KY. Efficacy of Microsurgical Treatment of Primary Lymphedema: A Systematic Review. *Ann Plast Surg* 2022;88:195-9.

b) Spörlein A, Will PA, Kilian K, Gazyakan E, Sacks JM, Kneser U, *et al.* Lymphatic Tissue Engineering: A Further Step for Successful Lymphedema Treatment. *J Reconstr Microsurg* 2021;37:465-74.

c) Hanson SE, Chang EI, Schaverien MV, Chu C, Selber JC, Hanasono MM, *et al.* Controversies in Surgical Management of Lymphedema. *Plast Reconstr Surg Glob Open* 2020;8:e2671.

d) Schaverien MV, Coroneos CJ. Surgical Treatment of Lymphedema. *Plast Reconstr Surg* 2019;144:738-58.

## 6. Lymphedema prevention

### Query used for the literature search

(lymphedema[MeSH Terms]) AND prevention

### Main findings

Lymphedema has been found reciprocally associated with obesity.<sup>353</sup> The prevention of one influences the other. This concept leads to the importance of the activation of the lower limb muscle pumps, together with the thoraco-abdominal ones, by means of properly conducted physical exercise protocols.<sup>354</sup> In this context, the aquatic environment can offer a significant benefit based on the buoyancy and on the natural graduated compression generated by the water, facilitating movements impeded in the dryland, particularly in obese and elderly patients. Lymphedema can be secondary to trauma. In case it is surgical, preoperative mapping and minimization of the tissue insult can reduce the lymphatic damage risk. This has been demonstrated also in the lower limb venous surgery context: a finding that is paving the way for further investigations dedicated to identifying the less aggressive approach to chronic ve-



nous disease in terms of lymphatic damage. Indeed, together with the surgical insult, the inflammatory consequences of thermal or chemical treatments should be properly assessed in patients potentially affected by both a venous and lymphatic component.<sup>355</sup> Graduated compression demonstrated a role in reducing the risk of lower limb lymphedema, but further wider studies are needed to come to a statistically significant conclusion regarding its preventive role. Considering the recurrent and chronic lymphedema nature, proper patient education, skincare and surveillance programs are mandatory in the disease prevention.<sup>356</sup>

#### *Analyzed literature possible biases*

Potentially heterogeneous study populations in terms of life-style habits.

#### *Suggested next research lines*

Prospective investigations on life-style factors influencing lymphedema prevention.

#### *Related statement in layman's term for public vein-lymphatic awareness*

Prevention of lymphedema is crucial and possible by appropriate skin hygiene, healthy lifestyle, compression tools use and adequate follow-up visits, always supervised by expert health-professionals.

#### *Suggested pertinent extra readings*

a) Wu X, Liu Y, Zhu D, Wang F, Ji J, Yan H. Early prevention of complex decongestive therapy and rehabilitation exercise for prevention of lower extremity lymphedema after operation of gynecologic cancer. *Asian J Surg* 2021;44:111-5.

b) Wang X, Ding Y, Cai HY, You J, Fan FQ, Cai ZF, *et al.* Effectiveness of modified complex decongestive physiotherapy for preventing lower extremity lymphedema after radical surgery for cervical cancer: a randomized controlled trial. *Int J Gynecol Cancer* 2020;30:757-63.

c) Spörlein A, Will PA, Kilian K, Gazyakan E, Sacks JM, Kneser U, *et al.* Lymphatic Tissue Engineering: A Further Step for Successful Lymphedema Treatment. *J Reconstr Microsurg* 2021;37:465-74.

d) Johansson K, Hayes S. A historical account of the role of exercise in the prevention and treatment of cancer-related lymphedema. *Lymphology* 2020;53:55-62.

## **7. Lymphedema differential diagnosis**

### *Query used for the literature search*

(lymphedema[MeSH Terms]) AND (differential diagnosis [MeSH Terms])

(lymphedema[MeSH Terms]) AND (diagnosis[MeSH Terms])

### *Main findings*

In order to perform a proper differential diagnosis first of all a proper lymphedema definition is needed: it can be identified as a chronic disease characterized by increased lymphatic fluid accumulation lasting for more than three months, causing swelling, leading to progressive tissue fibrosis and damage. Histology is not providing any pathognomonic finding, but it may include dermal infiltration, hyperkeratosis, epidermal papillomatosis, dermal vessel walls hypertrophy, fibroblasts hyperplasia.<sup>357</sup> A detailed history and physical examination are mandatory for properly guiding the diagnosis. Laboratory exams can identify eventual renal or hepatic causes of lymphedema, together with eventual infections. Ultrasound scanning can detect a venous origin of the edema (chronic venous disease and/or thrombosis), while also depicting the subcutaneous fluid infiltration and the eventual lymphnodes involvement.<sup>358</sup> Lymphoscintigraphy can confirm the diagnosis, while computed tomography and magnetic resonance can also identify causes of secondary lymphedema origin (masses) while investigating the soft tissue compromise. Bioimpedance represents a valuable opportunity to measure in an objective way the fluid shift in the edema differential diagnosis.<sup>359</sup> Systemic causes of lower limb edema include idiopathic cyclic edema, heart/liver/renal failure and malnutrition states. Venous system insufficiency is tightly interconnected with the lymphatic system function and can mutually influence the limb drainage. Infections, inflammatory states (for example arthritis), ischemia, lipedema, vascular malformations, tumors and trauma can lead to leg edema.<sup>360</sup> The heterogeneity of the above-described clinical scenario clearly indicates the need of a multi-specialty approach.

### *Analyzed literature possible biases*

Lack of precise methodology to discriminate between purely venous and lymphatic edema.

### *Suggested next research lines*

Identification of pathognomonic findings of venous vs. lymphatic edema.

### *Related statement in layman's term for public vein-lymphatic awareness*

In the diagnosis of lymphedema always exclude heart and renal conditions, malnutrition, malformations, tumors, lipedema, arterial and venous disease and post-traumatic swelling.

*Suggested pertinent extra readings*

- a) Rockson SG. Bioimpedance Analysis of Lower Extremity Lymphedema. *Lymphat Res Biol* 2020;18:98.
- b) Steele ML, Janda M, Vagenas D, Ward LC, Cornish BH, Box R, *et al.* A Bioimpedance Spectroscopy-Based Method for Diagnosis of Lower-Limb Lymphedema. *Lymphat Res Biol* 2020;18:101-9.
- c) Greene AK, Goss JA. Diagnosis and Staging of Lymphedema. *Semin Plast Surg* 2018;32:12-6.

**8. Lipedema signs, symptoms and diagnostic work-up**

*Query used for the literature search*

(lipedema[MeSH Terms]) AND ((signs[MeSH Terms]) OR (symptoms[MeSH Terms]))

*Main findings*

Lipedema is a chronic soft tissue disease affecting mainly, but not only, women. Its progressive nature is not yet fully confirmed by scientific evidence. The condition is characterized by a bilateral disproportion in fat distribution, accumulating on the extremities, sparing the trunk, hands and feet. Three clinical stages of progressive severity are identified:

- thickened soft subcutis, with small palpable nodules and a smooth skin surface;
- thickened soft subcutis, with larger nodules and an uneven skin surface;
- thickened hard subcutis, with large nodules and disfiguring fat deposition.

Another classification is defined by the topographical fat anomaly distribution:

- buttock;
- thigh;
- entire lower limb;
- arm;
- below knee.

Despite lipedema was first described in 1940, its detection and proper management remains globally suboptimal.<sup>361</sup> A genetic predisposition is supposed following the reported familial clusters. It usually appears during puberty, suggesting a estrogen-mediated component. The anomaly leads to adipocytes hyperplasia and/or hypertrophy. The inflammatory condition is also associated with a micro-angiopathy of the blood and lymphatic vessel, therefore potentially overlapping a lymphedema condition. The related endothelial inflammation and capillary damage can explain the hematoma tendency of this condition. The same inflammation is considered responsible of the neural

hypersensitivity to nociceptive stimuli, typical of lipedema. The quality of life is potentially severely affected by the condition.<sup>362</sup> The diagnosis is mainly clinical: bilateral, symmetrical, disproportionate fatty tissue hypertrophy, not involving hands and feet, associated with hypersensitivity to pressure pain and hematoma tendency. Stemmer sign is usually negative, but it can become positive if associated with a lymphedema condition.<sup>340</sup> Hepatic and renal function should always be assessed, together with all the causes of hormonal distress potentially mimicking lipedema. Diagnostic exams such as ultrasound, computed tomography, magnetic resonance, bioimpedance, lymphography can be of help in the differential diagnosis, but they present no pathognomonic outcome for lipedema.<sup>363</sup>

*Analyzed literature possible biases*

Lack of homogenous populations for lipedema pathognomonic diagnostic findings.

*Suggested next research lines*

Blind investigations on pure lipedema patients.

*Related statement in layman's term for public vein-lymphatic awareness*

Leg swelling leg can be caused by fat tissue alteration (lipedema). The condition affects both limbs, it spares the feet and hands and it is associated with pain at pressure on the skin.

*Suggested pertinent extra readings*

- a) Herbst KL, Kahn LA, Iker E, Ehrlich C, Wright T, McHutchison L, *et al.* Standard of care for lipedema in the United States. *Phlebology* 2021;36:779-96.
- b) Bertlich M, Jakob M, Bertlich I, Schiff R, Bertlich R. Lipedema in a male patient: report of a rare case - management and review of the literature. *GMS Interdiscip Plast Reconstr Surg DGPW* 2021;10:Doc11.
- c) Angst F, Benz T, Lehmann S, Sandor P, Wagner S. Common and Contrasting Characteristics of the Chronic Soft-Tissue Pain Conditions Fibromyalgia and Lipedema. *J Pain Res* 2021;14:2931-41.
- d) Torre YS, Wadea R, Rosas V, Herbst KL. Lipedema: friend and foe. *Horm Mol Biol Clin Investig.* 2018;33:/j/hmbci.2018.33.issue-1/hmbci-2017-0076/hmbci-2017-0076.xml.

**9. Lipedema treatment**

*Query used for the literature search*

(lipedema[MeSH Terms]) AND ((signs[MeSH Terms]) OR (symptoms[MeSH Terms]))

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### Main findings

Lipedema is a chronic condition requiring life-style adaptation. Diet and exercise are part of the conservative management of the disease. Nevertheless, no specific nutritional regimen or physical exercise protocol have been already validated scientifically. Considering obesity is often associated with lipedema, weight control is indicated among the first treatment measures. Preliminary evidence suggest ketogenic diet can help in lipolysis, therefore in lipedema management.<sup>364</sup> Exercises activating the leg muscle pump and consequently facilitating the lymphatic drainage might be of help in reducing the inflammatory lipedema state, nevertheless properly designed standardized physical activities have not been reported yet in the literature. The aquatic environment could represent an advantage for this kind of patients, considering the graduated compression effect associated with the immersion. The same graduated compression can be applied to facilitate fluids drainage and inflammation control. In case of significant limb shape asymmetry, a flat knit must be taken into consideration.<sup>363</sup> The impact of lipedema on health-related quality of life and on the psychological status must not be underestimated: data show a significant deterioration in these patients and further studies are encouraged to identify validated and adapted measures related to the topic.<sup>365</sup> In case of failure of the conservative treatment, liposuction can be taken into consideration, after careful evaluation of the specialist. Pain, cramps, itching, edema and bruising demonstrated to potentially improve after liposuction, but large randomized comparative trial with mid-long term follow-up are needed before giving high grade recommendation and clear indication to the procedure.<sup>366</sup> To our knowledge, no specific drugs or topicals demonstrated an evidence-based benefit in the management of lipedema.

### Analyzed literature possible biases

Lack of homogeneity in lipedema stages inclusion in the study populations.

### Suggested next research lines

Randomized comparative trials on lipedema treatment options.

### Related statement in layman's term for public vein-lymphatic awareness

Lipedema conservative management is similar to lymphedema one and require highly specialized health-professionals. Specifically dedicated liposuction techniques can be taken into consideration if conservative measure-

ment alone failed and must be performed by expert professionals.

### Suggested pertinent extra readings

a) Schmidt J, Kruppa P, Georgiou I, Ghods M. Management of large volume liposuction in lipedema patients with von Willebrand disease: A systematic review and treatment algorithm. *Clin Hemorheol Microcirc* 2021;78:311-24.

b) Esmer M, Schingale FJ, Unal D, Yazıcı MV, Güzel NA. Physiotherapy and rehabilitation applications in lipedema management: A literature review. *Lymphology* 2020;53:88-95.

c) Aksoy H, Karadag AS, Wollina U. Cause and management of lipedema-associated pain. *Dermatol Ther* 2021;34:e14364.

d) Dudek JE, Białaszek W, Ostaszewski P, Smidt T. Depression and appearance-related distress in functioning with lipedema. *Psychol Health Med* 2018;23:846-53.

### 10. Lymphedema-lipedema follow-up protocol

#### Query used for the literature search

(lymphedema) AND (follow up studies)

(lipedema) AND (follow up studies)

### Main findings

Differently from the upper limb post-mastectomy lymphedema, detailed surveillance protocols are missing for the lower limb, as well as for the lipedema.<sup>367</sup> Apart for the secondary lymphedema related to a specific removable cause, both conditions are currently considered incurable in a definitive way and associated with a permanent life-style adaptation. This must include skincare, dedicated exercise protocols, compression and infection prevention. A constant relationship with the specialist must be developed in order to detect recurrences or aggravations of the clinical condition. Self-management has a pivotal role in these patients, therefore proper awareness of the disease must be delivered to them by a multi-disciplinary pool of experts, including also the psychological component.<sup>368</sup> While there is no evidence-based data recommending a specific timeline for monitoring, it is this expert panel opinion at least yearly if not twice per year visits with the specialist should be encouraged to promptly detect recurrences, complications and aggravations. Patient compliance to disease management should be monitored for both eventual compression prescription and correct life-style acquisition. Compression garment should be renewed after the

## 10. LYMPHEDEMA - LIPEDEMA

Leg lymphatic drainage alteration (lymphedema) is so frequent and so often under-diagnosed to be called “the hidden epidemic”. Leg fat alteration (lipedema) is often confused with lymphedema. Evidence-based facts are reported below and at the dedicated website

[www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)



### LYMPHEDEMA - LIPEDEMA

1. Lymphedema is a chronic fluids accumulation. Lipedema is an inflammation of the leg fat tissue, possibly associated with lymphedema.
2. Lymphedema is a progressive disease whose stage must be precisely identified by an expert.
3. Lymphedema can manifest as swelling, redness, skin infections, abnormal tissue proliferation. At least ultrasound scanning must be performed, eventually together with more advanced techniques based on the specific case.
4. Lymphedema management includes conservative multi-specialty expert assessment, validated protocols of patients education, skin hygiene, compression, mechanical lymphatic drainage, specific physical exercises. Mesotherapy is not a validated option. No drug has been currently validated to increase lymphatic drainage, including diuretics.
5. Lymphedema surgical treatment must be performed only in highly experienced centers and once the conservative approach have demonstrated to be insufficient.
6. Prevention of lymphedema is crucial and possible by appropriate skin hygiene, healthy lifestyle, compression tools use and adequate follow-up visits, always supervised by expert health-professionals.
7. In the diagnosis of lymphedema always exclude heart and renal conditions, malnutrition, malformations, tumors, lipedema, arterial and venous disease and post-traumatic swelling.
8. Leg swelling leg can be caused by fat tissue alteration (lipedema). The condition affects both limbs, it spares the feet and hands and it's associated with pain at pressure on the skin
9. Lipedema conservative management is similar to lymphedema one and require highly specialized health-professionals. Specifically dedicated liposuction techniques can be taken into consideration if conservative measurement alone failed and must be performed by expert professionals.
10. Lymphedema-lipedema most often become chronic: they generally require lifelong care and proper support by expert health-professionals.

Figure 10.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding lymphedema and lipedema.

specific time recommended by the producer in order not to lose its efficacy.<sup>369</sup> Considering the tight interconnection between lymphatic and venous system and the potential implications in the adipose tissue, a detailed visit should be accompanied by a vascular ultrasound scanning whenever considered appropriate by the assessing specialist. Future research lines should be addressed to identify the proper timing for the lower limb lymphedema and lipedema clinical and instrumental surveillance (Figure 10).

### Analyzed literature possible biases

Lack of investigations on different surveillance protocols for both lymphedema and lipedema.

### Suggested next research lines

Identification of best follow-up and surveillance protocols for both lymphedema and lipedema.

### Related statement in layman’s term for public vein-lymphatic awareness

Lymphedema-lipedema most often become chronic: they generally require lifelong care and proper support by expert health-professionals.

### Suggested pertinent extra readings

a) Dalal A, Eskin-Schwartz M, Mimouni D, Ray S, Days W, Hodak E, *et al.* Interventions for the prevention of recurrent erysipelas and cellulitis. *Cochrane Database Syst Rev* 2017;6:CD009758.

b) Carl HM, Walia G, Bello R, Clarke-Pearson E, Hasanein AH, Cho B, *et al.* Systematic Review of the Surgical Treatment of Extremity Lymphedema. *J Reconstr Microsurg* 2017;33:412-25.

c) Scaglioni MF, Arvanitakis M, Chen YC, Giovanoli P, Chia-Shen Yang J, Chang EI. Comprehensive review of vascularized lymph node transfers for lymphedema: Outcomes and complications. *Microsurgery* 2018;38:222-9.

## 11. Sclerotherapy and esthetic phlebology

### 1. Sclerotherapy safety

#### Query used for the literature search

(sclerotherapy) AND (safety)

#### Main findings

Following the use of properly validated drugs and injection method, sclerotherapy is safe, yet complications can arise in not expert hands. Proper training of the professionals practicing sclerotherapy is mandatory to guarantee safety and efficacy of the procedure.<sup>370</sup> Polidocanol and sodium-tetradecyl-sulfate are the most investigated and used sclerotherapy agents. A systematic review reported a significantly higher complication rate following the use of absolute ethanol in sclerotherapy of vascular malformations.<sup>151</sup> An analysis of the World Health Organization pharmacovigilance database reported different safety profiles for different sclerosing agents: polidocanol is associated with more reporting of venous embolic/thrombotic events, ethanalamine with cardiac arrhythmias and sodium tetradecyl sulfate with allergic reactions. Further properly collected clinical data are needed to confirm these findings.<sup>371</sup> A 2021 Cochrane analysis on 28 randomized controlled trials, involving 4278 participants, pointed out the need of producing homogenous data, using standardized sclerosant doses, focusing on objective outcomes. No significant differences in the safety of the different sclerosant agents concentrations has been reported.<sup>372</sup>

*Analyzed literature possible biases*

Heterogenous final drug concentration in the blood stream due to not specified hemodynamics and number of injections.

*Suggested next research lines*

Safety assessment in different drug concentrations, vessel calibers and related hemodynamics.

*Related statement in layman's term for public vein-lymphatic awareness*

Sclerotherapy is a safe effective therapy for leg veins affected by chronic venous disease, provided it is performed by experts professionals.

*Suggested pertinent extra readings*

a) Davies HO, Watkins M, Oliver R, Berhane S, Bradbury AW. Adverse neurological events after sodium tetradecyl sulfate foam sclerotherapy - A prospective, observational study of 8056 treatments. *Phlebology* 2022;37:97-104.

b) Marcoux S, Théorêt Y, Dubois J, Essouri S, Pincivy A, Coulombe J, *et al.* Systemic, local, and sclerotherapy drugs: What do we know about drug prescribing in vascular anomalies? *Pediatr Blood Cancer* 2021;68:e29364.

c) Li N, Li J, Huang M, Zhang X. Efficacy and safety of polidocanol in the treatment of varicose veins of lower extremities: A protocol for systematic review and meta-analysis. *Medicine (Baltimore)* 2021;100:e24500.

d) Lim SY, Tan JX, D'Cruz RT, Syn N, Chong TT, Tang TY. Catheter-directed foam sclerotherapy, an alternative to ultrasound-guided foam sclerotherapy for varicose vein treatment: A systematic review and meta-analysis. *Phlebology* 2020;35:369-83.

**2. Foam sclerotherapy production validated method**

*Query used for the literature search*

((foam) AND (sclerotherapy)) AND (production)

*Main findings*

Foam sclerotherapy represents a pillar in chronic venous disease treatment. Its production method is of paramount importance to guarantee safety, efficacy, standardization and reproducibility of the result. The two main sclerosing agents for foam production are polidocanol and sodium tetradecyl sulfate. Foam can be produced by physician compounded or by automatic methods. Foam physical properties can vary based on the syringe and needle features, as well as liquid/air ratio and production method. The cur-

rently most commonly used method is the Tessari one, whose standardization and reproducibility has been demonstrated by Watkins *et al.*<sup>373</sup> Automated foam production methods have been reported in the literature but, up to our knowledge, not in a head to head comparison with physician compounded production, therefore the clinical benefit cannot be determined.<sup>374, 375</sup> A recent large study on 8056 patients treated by foam sclerotherapy confirmed the procedure safety with a very low incidence of neurological adverse events. Migraine history, physiological gas use and foam volume increased the risk of these complications.<sup>376</sup>

*Analyzed literature possible biases*

Materials (syringes, needles, etc) not always specified in the related papers.

*Suggested next research lines*

Head to head comparison between compounded and not compounded foam.

*Related statement in layman's term for public vein-lymphatic awareness*

Foam produced by expert hands, using proper syringes and method is standardized, reproducible, safe and effective.

*Suggested pertinent extra readings*

a) Meghdadi A, Jones SA, Patel VA, Lewis AL, Millar TM, Carugo D. Foam-in-vein: A review of rheological properties and characterization methods for optimization of sclerosing foams. *J Biomed Mater Res B Appl Biomater* 2021;109:69-91.

b) Bottaro E, Paterson J, Zhang X, Hill M, Patel VA, Jones SA, *et al.* Physical Vein Models to Quantify the Flow Performance of Sclerosing Foams. *Front Bioeng Biotechnol* 2019;7:109.

c) Tan L, Wong K, Connor D, Fakhim B, Behnia M, Parsi K. Generation of sclerosant foams by mechanical methods increases the foam temperature. *Phlebology* 2017;32:501-5.

d) Cameron E, Chen T, Connor DE, Behnia M, Parsi K. Sclerosant foam structure and stability is strongly influenced by liquid air fraction. *Eur J Vasc Endovasc Surg* 2013;46:488-94.

**3. Sclerotherapy indications and contraindications in chronic venous disease**

*Query used for the literature search*

((sclerotherapy) AND (indication)) OR ((sclerotherapy) AND (contraindication))

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### Main findings

International guidelines present a general agreement in the indications of lower limb varicose veins treatment by sclerotherapy, extending it to the whole spectrum of the disease, from CEAP clinical class 1 to 6, even if with differences in the grades of recommendation and in the maximum volume allowed. While all the international documents agree in the allergy to the sclerosing agent as a contraindication, discrepancies are identified for the other possible factors. While no clear evidence-based data has been produced on the topic, expert opinion suggests particular post-procedural care in avoiding immediate mobilization of the patient and sudden Valsalva maneuver as this could facilitate vasospasm-related complication onset.<sup>7</sup> Recent guidelines included also the sclerotherapy indication for the treatment of pelvic venous escape points. Nevertheless, no clear indications are available regarding neither the hemodynamic features of the targeted vessels nor the related drug concentration and volume.<sup>120</sup> A review reported sclerotherapy safety during pregnancy, but it must be avoided during the first trimester and the last 4 weeks of pregnancy. Further data are needed to provide a proper recommendation in this context.<sup>377</sup> Apart lower limb varicose veins, sclerotherapy use has been suggested for treatment of the face, hand and chest region. Particular care should be used in these districts, especially on the face, as severe complications might arise and a lack of supporting literature is present up to the authors knowledge.<sup>378</sup>

### Analyzed literature possible biases

Outcome measures mainly focused on anatomical recurrence rather than also patient reported outcome and cost-effectiveness.

### Suggested next research lines

Homogeneous international indication and contraindication delivery.

### Related statement in layman's term for public vein-lymphatic awareness

Sclerotherapy is indicated in all stages of leg chronic venous disease. It is absolutely contraindicated in case of known allergy to the sclerosant drug, acute deep venous thrombosis and pulmonary embolism, local infection in the injection area or systemic infection, long-lasting immobility, known symptomatic right to left shunt in case of foam formulation. An expert physician must assess the single case for eligibility to sclerotherapy.

### Suggested pertinent extra readings

a) de Ávila Oliveira R, Riera R, Baptista-Silva JC. Injection sclerotherapy for varicose veins. *Cochrane Database Syst Rev* 2021;12:CD001732.

b) Nakano LC, Cacione DG, Baptista-Silva JC, Fluminan RL. Treatment for telangiectasias and reticular veins. *Cochrane Database Syst Rev* 2021;10:CD012723.

c) Chwała M, Szczeklik W, Szczeklik M, Aleksiejew-Kleszczyński T, Jagielska-Chwała M. Varicose veins of lower extremities, hemodynamics and treatment methods. *Adv Clin Exp Med* 2015;24:5-14.

d) Rabe E, Breu FX, Cavezzi A, Coleridge Smith P, Frullini A, Gillet JL, *et al.*; Guideline Group. European guidelines for sclerotherapy in chronic venous disorders. *Phlebology* 2014;29:338-54.

## 4. Sclerotherapy induced hyperpigmentation management

### Query used for the literature search

(sclerotherapy) AND (hyperpigmentation)

### Main findings

Hyperpigmentation after sclerotherapy for lower limb chronic venous disease has been reported in over 20% of cases and considered transient in the majority of cases.<sup>379</sup> While an expert vein center should not experience such high incidence, the issue exists and requires proper management. Already in the nineties Thibault *et al.* described the patho-physiology of the phenomenon as related to the serum ferritin and the possibility of resolution by means of copper vapor laser.<sup>380</sup> Skin iron deposition has been known in vein pathophysiology for a long time and topical iron chelation proposed consequently.<sup>381</sup> Nevertheless, despite topical products claims, an evidence based potential benefit in their use is still missing properly collected data and scientific publications, up to the knowledge of the author. Both MPFF<sup>382</sup> and Sulodexide,<sup>274</sup> two venous active oral drugs, reported an associated lower incidence of post-sclerotherapy hyperpigmentation, suggesting a multifactorial component triggering the same hyperpigmentation phenomenon. Future investigations on the topic are needed and, in order to move forward in a scientifically validated way, providing an objective assessment of the hyperpigmentation is mandatory. Indeed, the assessment can be currently influenced by the skin type and lack of properly validated scores. A preliminary proposal has been recently done by means of a dedicated software and related "hyperpigmentation index".<sup>383</sup>

*Analyzed literature possible biases*

Lack of objective hyperpigmentation assessment tools.

*Suggested next research lines*

Validation of an internationally recognized hyperpigmentation score.

*Related statement in layman's term for public vein-lymphatic awareness*

Up to 20% of cases can present post-injection hyperpigmentation. The phenomenon is usually transient.

*Suggested pertinent extra readings*

a) Nakano LC, Cacione DG, Baptista-Silva JC, Fluminian RL. Treatment for telangiectasias and reticular veins. *Cochrane Database Syst Rev* 2021;10:CD012723.

b) Bi M, Li D, Chen Z, Wang Y, Ren J, Zhang W. Foam sclerotherapy compared with liquid sclerotherapy for the treatment of lower extremity varicose veins: A protocol for systematic review and meta analysis. *Medicine (Baltimore)* 2020;99:e20332.

c) Yiannakopoulou E. Safety Concerns for Sclerotherapy of Telangiectases, Reticular and Varicose Veins. *Pharmacology* 2016;98:62-9.

d) Hamdan A. Management of varicose veins and venous insufficiency. *JAMA* 2012;308:2612-21.

**5. Sclerotherapy periprocedural management**

*Query used for the literature search*

(periprocedural) AND (sclerotherapy)

*Main findings*

Allergic reactions following sclerotherapy of the lower limb varicose veins are extremely rare, therefore no fasting need is usually recommended before an injection.<sup>311</sup> After the procedure graduated compression is recommended in a heterogeneous way in the different guidelines.<sup>7</sup> A recent review reported that post-sclerotherapy compression may bring clinical benefits at short-term follow-up. Nevertheless, more data are needed to identify proper type, class, length, and duration of compression.<sup>384</sup> As for all varicose vein procedures, a careful thrombotic risk assessment must be performed in all patients. Compared to other procedures, sclerotherapy did not show an increased risk of thrombosis and it actually demonstrated a lower incidence of deep venous thrombosis in the first 30 days.<sup>385</sup> No strong evidence-based data can be found by the authors regarding the real need of avoiding ultra-violet exposure after sclerotherapy. Yet, caution should be applied,

particularly in the high melanin content skin types. The authors were not able to identify literature specifying in an evidence-based way both the physical activity and the flying restrictions following sclerotherapy injection. On an empirical basis, Valsalva maneuver should be avoided right after the injection, while a normal physical activity can be restored few hours later, having care in avoiding direct leg trauma or forced limb position that might hamper a physiological drainage. Flying after the procedure should be associated with the awareness of the related dehydration and blood viscosity risk increase, leading to proper patient hydration, eventual compression stockings use and physical activity on board. Further data are needed on this topic before releasing significant recommendations.

*Analyzed literature possible biases*

- Heterogeneous investigations in compression use.
- Lack of data on periprocedural life-style.

*Suggested next research lines*

Post-sclerotherapy sun exposure, long distance flights and lifestyle.

*Related statement in layman's term for public vein-lymphatic awareness*

Sclerotherapy injection must be accompanied by proper patient thrombotic risk assessment and life-style adaptation as per the evaluation of the expert physician.

*Suggested pertinent extra readings*

a) De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, *et al.* European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg* 2022;63:184-267.

b) Bayer A, Kuznik N, Langan EA, Recke A, Recke AL, Faerber G, *et al.* Clinical outcome of short-term compression after sclerotherapy for telangiectatic varicose veins. *J Vasc Surg Venous Lymphat Disord* 2021;9:435-43.

c) Campos Gomes CV, Prado Nunes MA, Navarro TP, Dardik A. Elastic compression after ultrasound-guided foam sclerotherapy in overweight patients does not improve primary venous hemodynamics outcomes. *J Vasc Surg Venous Lymphat Disord* 2020;8:110-7.

d) Zubac D, Buoite Stella A, Morrison SA. Up in the Air: Evidence of Dehydration Risk and Long-Haul Flight on Athletic Performance. *Nutrients* 2020;12:2574.

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## 6. Sclerotherapy and laser for C1 patients: indications and technical notes

### Query used for the literature search

((indications)) AND (teleangectasia) AND ((laser) OR (sclerotherapy))

### Main findings

International guidelines generally agree in considering sclerotherapy as the first line indication for CEAP C1 patients treatment, even if heterogeneity exists in the recommendation grade. A general agreement is found in the need of proper pre-treatment history and ultrasound scanning performance. Transdermal laser can be taken into consideration in case of allergy to the sclerosant, previous sclerotherapy side effects, needle-phobia. The skin type, the size and depth of the vessel is guiding the choice of the wavelength, of the spot size and of the radiant exposure. Laser treatment can be effective but no solid data demonstrate a superiority to sclerotherapy injection, while its performance is associated with potential significant periprocedural pain.<sup>7</sup> A new trend toward multi-wavelengths combination showed preliminary valuable outcomes to be confirmed in long follow-up and properly randomized studies.<sup>386</sup> A synergy between laser and sclerotherapy has been standardized under the method Crio Laser Crio Sclerotherapy with preliminary excellent aesthetic outcomes, to be validated in properly conducted randomized comparative trials.<sup>387</sup> A recent Cochrane revision reported no superiority of any sclerosant compared to another or to laser. Low evidence suggest polidocanol might cause less pain, sodium tetradecyl sulfate more hyperpigmentation and matting.<sup>20</sup> Properly designed studies are needed to obtain a more evidence-based and reliable conclusion.

### Analyzed literature possible biases

Heterogeneous data collection in terms of sclerotherapy and laser methodology and objective outcome measures.

### Suggested next research lines

Different sclerosants and lasers head to head comparison in homogeneous study populations.

### Related statement in layman's term for public vein-lymphatic awareness

Sclerotherapy is the first-line treatment for leg anti-aesthetic veins. Specific lasers use can be taken into consideration for vessel smaller than 1 mm.

### Suggested pertinent extra readings

a) De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, *et al.* Editor's Choice - European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur J Vasc Endovasc Surg* 2022;63:184-267.

b) Gibson K, Gunderson K. Liquid and Foam Sclerotherapy for Spider and Varicose Veins. *Surg Clin North Am* 2018;98:415-29.

c) Watson JJ, Mansour MA. Cosmetic sclerotherapy. *J Vasc Surg Venous Lymphat Disord* 2017;5:437-45.

d) Meesters AA, Pitassi LH, Campos V, Wolkerstorfer A, Dierickx CC. Transcutaneous laser treatment of leg veins. *Lasers Med Sci* 2014;29:481-92.

## 7. C1 laser treatment complications management

### Query used for the literature search

(laser) AND (transdermal) AND (complication)

### Main findings

Transdermal lasers for lower limb teleangectasias and reticular veins treatment require proper deep knowledge of the device, setting, clinical and hemodynamic scenario. Appropriate device type and patient selection is fundamental to avoid complications. Most common complications are burns, scarring, dyspigmentation, ocular injury, and infection. Burns can be the consequence of wrong setting leading to an excessive energy delivery. Another cause can be found in the improper use of cooling devices. A procedural sudden graying of the treated area suggests an overheating for which energy delivery should be stopped immediately. Crusts and ulcerations can appear days after the procedure and can represent a preliminary sign of further scarring and dyspigmentation. Careful balance in distancing the spots of energy delivery is important to avoid overheating as well as discontinuous treatment areas. Emollients and topical steroids can help the healing process.<sup>388</sup> The eventual damage of the skin protective layer can favor infections: a related drug therapy is to be initiated promptly.<sup>389</sup> Dyspigmentation in laser treatment can be characterized hypopigmentation and hyperpigmentation. The risk is higher in dark skinned and/or intensely tanned patients. Hypopigmentation can be covered by makeup or treated by melanin release stimulation by means of fractionated CO2 laser or narrow-band ultraviolet light treatments.<sup>390</sup> Ultraviolet exposition for at least 2 weeks after the treatment is suggested. Superficial chemical peels and



hydroquinone can favor the hyperpigmentation resolution. Accidental exposure of health professionals and patients to the laser emission must be taken into consideration as well. Use of a certified room and protective glasses is mandatory.<sup>391</sup>

*Analyzed literature possible biases*

Unspecified operator expertise. Heterogeneous device settings.

*Suggested next research lines*

RCT on laser complications treatment options.

*Related statement in layman's term for public vein-lymphatic awareness*

Laser treatment of leg anti-aesthetic veins must be performed by highly expert physicians limiting possible complications such as skin burns and pigmentations.

*Suggested pertinent extra readings*

a) Isedeh P, Kohli I, Al-Jamal M, Agbai ON, Chaffins M, Devpura S, *et al.* An in vivo model for postinflammatory hyperpigmentation: an analysis of histological, spectroscopic, colorimetric and clinical traits. *Br J Dermatol* 2016;174:862-8.

b) Adamič M, Palmetun-Ekbäck M, Boixeda P. 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.

c) Alam M, Warycha M. Complications of lasers and light treatments. *Dermatol Ther.* 2011;24:571-80.

d) Metelitsa AI, Alster TS. Fractionated laser skin resurfacing treatment complications: a review. *Dermatol Surg* 2010;36:299-306.

**8. Carboxytherapy / ozone therapy evidence in venous-lymphatic disease management**

*Query used for the literature search*

carboxytherapy / (ozone therapy) AND ((vein) OR (venous))

*Main findings*

Nowadays, carboxytherapy and ozone therapy for lower limb aesthetic treatments are on fashion in a progressively increasing number of countries and many commercials are found claiming a benefit in the early stages of lower limb venous and lymphatic disease. In reality, both carboxytherapy and ozone therapy have been in the market for decades, yet no solid evidence based data have been found

in support of this use. Our literature search reports just a limited literature for both carboxytherapy<sup>392</sup> and ozone therapy potential benefit and just for wound healing.<sup>393</sup> Also in the ulcer context, more data and randomized comparative trials are needed before recommending the use of both carboxytherapy and ozone therapy. More research is also needed to explain and prove the mechanism of action of both carboxytherapy and ozone therapy in the context of aesthetic phlebology. While generally considered safe, these therapeutic approaches should be properly tested and monitored, as potential serious complications have been also reported.<sup>394</sup> Both health and non-health professionals should be adequately informed about the lack of evidence in support of both carboxytherapy and ozone therapy for venous-lymphatic disorders.

*Analyzed literature possible biases*

No significant literature available.

*Suggested next research lines*

Properly conducted clinical trials in vein-lymphatic patients.

*Related statement in layman's term for public vein-lymphatic awareness*

Up to the knowledge of this experts consensus, carboxytherapy and ozone therapy have not demonstrated to improve venous-lymphatic function and appearance.

*Suggested pertinent extra readings*

a) Zhou YT, Zhao XD, Jiang JW, Li XS, Wu ZH. Ozone Gas Bath Combined with Endovenous Laser Therapy for Lower Limb Venous Ulcers: A Randomized Clinical Trial. *J Invest Surg* 2016;29:254-9.

b) Solovăstru LG, Sfîncanu A, De Ascentii A, Cappare G, Mattana P, Vâță D. Randomized, controlled study of innovative spray formulation containing ozonated oil and  $\alpha$ -bisabolol in the topical treatment of chronic venous leg ulcers. *Adv Skin Wound Care* 2015;28:406-9.

**9. Radiofrequency evidence in venous-lymphatic disease management**

*Query used for the literature search*

(radiofrequency) AND ((teleangectasia) OR (spider veins) OR (reticular veins))

*Main findings*

Low energy percutaneous radiofrequency thermocoagulation has been used for many years now among the lower

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limb teleangectasias available treatment options.<sup>395</sup> The gold standard remains sclerotherapy, but radiofrequency was compared also to transdermal laser, showing a possible valuable alternative in specific cases characterized by small and superficial vessels.<sup>396</sup> The literature is lacking properly conducted double-blind controlled clinical trials comparing the different laser modalities, therefore high grade recommendations cannot be done in favor of a specific laser or radiofrequency type, still leaving the gold standard role to sclerotherapy.<sup>388</sup> Recently, radiofrequency has shown a potential role in synergy with sclerotherapy, but further investigations are needed.<sup>397</sup>

*Analyzed literature possible biases*

No significant literature available.

*Suggested next research lines*

Properly conducted clinical trials in vein-lymphatic patients.

*Related statement in layman's term for public vein-lymphatic awareness*

Thermal coagulation of the vein can be an option in aesthetic leg vein treatment, but further data are needed before recommending it over sclerotherapy.

*Suggested pertinent extra readings*

a) Nakano LCU, Cacione DG, Baptista-Silva JC, Flumignan RL. Treatment for telangiectasias and reticular veins. Cochrane Database Syst Rev 2017;2017:CD012723.

**10. False claims in aesthetic phlebology**

*Query used for the literature search*

fake claims medicine

*Main findings*

In modern times, the culture of youth and beauty prevails. An “infodemic” is generated by commercials on products and treatments dedicated to improve the aesthetics, including leg veins appearance, delivering false claims.<sup>2</sup> Health and non health professionals should be informed that, according to the scientific literature, sclerotherapy remains the gold standard for lower limb aesthetic vein treatment and that laser and/or radiofrequency are not superior it. Potential synergy is developed by the combination of sclerotherapy and laser/radiofrequency, but solid scientific data are missing on the topic.<sup>20</sup> It is of paramount importance to rely only on expert physicians for the treatment, particularly considering teleangectasias and

**11. SCLEROTHERAPY + AESTHETIC PHLEBOLOGY**



Sclerotherapy is a safe and effective technique for therapeutic and aesthetic management of the leg veins. It remains the most frequently practiced approach around the world. Proper expertise is mandatory in its practice: indeed, poking a vein is an easy act many people can perform, while knowing where and how to poke and what to inject is a medical gesture requiring top knowledge. Similar consideration can be done for laser use in aesthetic phlebology: a growing practice, requiring proper expertise. Validated info are reported below and at the website:

[www.vvinfoundation.com/fake-news-free-project/](http://www.vvinfoundation.com/fake-news-free-project/)

**SCLEROTHERAPY and AESTHETIC PHLEBOLOGY**

1. Sclerotherapy is a safe effective therapy for leg veins affected by chronic venous disease, provided it is performed by experts professionals.
2. Foam produced by expert hands, using proper syringes and method is standardized, reproducible, safe and effective.
3. Sclerotherapy is indicated in all stages of leg chronic venous disease. It is absolutely contraindicated in case of known allergy to the sclerosant drug, acute deep venous thrombosis and pulmonary embolism, local infection in the injection area or systemic infection, long-lasting immobility, known symptomatic right to left shunt in case of foam formulation. An expert physician must assess the single case for eligibility to sclerotherapy.
4. Up to 20% of cases can present post-injection hyperpigmentation. The phenomenon is usually transient.
5. Sclerotherapy injection must be accompanied by proper patient thrombotic risk assessment and life-style adaptation as per the evaluation of the expert physician.
6. Sclerotherapy is the first-line treatment for leg anti-aesthetic veins. Specific lasers use can be taken into consideration for vessel smaller than 1 mm.
7. Laser treatment of leg anti-aesthetic veins must be performed by highly expert physicians limiting possible complications such as skin burns and pigmentations.
8. Up to the knowledge of this experts consensus, carboxytherapy and ozone therapy have not demonstrated to improve venous-lymphatic function and appearance.
9. Thermal coagulation of the vein can be an option in aesthetic leg vein treatment, but further data are needed before recommending it over sclerotherapy.
10. No aesthetic vein treatment can be considered definitive since venous disease can present recurrence. A proper ultrasound scanning should always precede an aesthetic vein treatment.

Figure 11.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding sclerotherapy and aesthetic phlebology.

reticular veins were found to be associated with deeper truncal varicosities in 26% of cases versus 14% in subjects without superficial hypertension signs.<sup>21</sup> Also for this reason, a detailed clinical visit and venous ultrasound scanning must always precede the aesthetic treatment, in order to avoid undertreatment of the underlying venous disease. A false claim to be avoided is the one reporting a permanent resolution of the aesthetic complaint. Venous hypertension recurrence was reported in more than 60% of cases and it must be considered para-physiological in bipeds constantly overwhelmed by the force of gravity and by the aging process.<sup>398</sup> Certainly, a proper aesthetic treatment should not be associated with a recurrence on the same or nearby anatomical districts in the short terms of few years. Proper lifestyle and follow-up visits with an expert physician are suggested to optimize the result and its perdurance (Figure 11).

*Analyzed literature possible biases*

Not applicable.

*Suggested next research lines*

Real world data on misinformation in venous-lymphatic disease.

*Related statement in layman's term for public vein-lymphatic awareness*

No aesthetic vein treatment can be considered definitive since venous disease can present recurrence. A proper ultrasound scanning should always precede an aesthetic vein treatment.

*Suggested pertinent extra readings*

a) Robledo I, Jankovic J. Media hype: Patient and scientific perspectives on misleading medical news. *Mov Disord* 2017;32:1319-23.

b) Koblenzer CS. Psychosocial aspects of beauty: how and why to look good. *Clin Dermatol* 2003;21:473-5.

**12. Lifestyle, sport, nutrition**

**1. Obesity, postural defects, physical inactivity impact on venous-lymphatic disease**

*Query used for the literature search*

((obesity) AND (risk factor)) AND ((venous) OR (lymphatic))

((weight bearing) AND (risk factor)) AND ((venous) OR (lymphatic))

((physical activity) AND (risk factor)) AND ((venous) OR (lymphatic))

**Main findings**

Obesity might impact venous and lymphatic lower limb drainage to have led to the term “Phlebesity.” Considering venous disorders affect potentially more than half of the population and obesity more than one quarter of it, the proper management of the condition is of paramount importance. A 2017 review demonstrated how obesity is an important risk factor for venous disease, and how obese patients affected by venous disease are more likely to be symptomatic. Moreover, obesity per se can represent a direct cause of venous hypertension.<sup>399</sup> Unfortunately, many investigations are including obesity in the exclusion criteria for enrollment, therefore important data on the topic are still missing and should be encouraged in their collection.<sup>400</sup> The way the weight is delivered on the feet is important as well in venous return pathophysiology. Indeed, a static foot dis-

order has been identified as a risk factor for chronic venous disease and vein-lymphatic experts are requested to assess also this aspect in their patient evaluation.<sup>401</sup> Activation of the lower limb muscular pump is of great importance as well. Perceived exertion, and quality of life is positively impacted by physical activity in venous disease patients. Yet, properly standardized and reproducible exercise protocols are still missing.<sup>402</sup> The importance of standardized exercise is seen also in the opposite effect of physical activity as a potential thrombo-embolic risk factor.<sup>403</sup>

*Analyzed literature possible biases*

- Exclusion of obese patients from many venous-lymphatic investigations.
- Not inclusion of static foot disorders as possible bias.
- Lack of standardization in physical activity.

*Suggested next research lines*

Investigations taking into consideration the above mentioned bias.

*Related statement in layman's term for public vein-lymphatic awareness*

Obesity, postural defects, physical inactivity are risk factors for leg chronic venous disease.

*Suggested pertinent extra readings*

a) Erdal ES, Demirgüç A, Kabalcı M, Demirtaş H. Evaluation of physical activity level and exercise capacity in patients with varicose veins and chronic venous insufficiency. *Phlebology* 2021;36:636-43.

b) Hall G, Laddu DR, Phillips SA, Lavie CJ, Arena R. A tale of two pandemics: How will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another? *Prog Cardiovasc Dis* 2021;64:108-10.

c) Lerebourg L, L'Hermette M, Menez C, Coquart J. The effects of shoe type on lower limb venous status during gait or exercise: A systematic review. *PLoS One* 2020;15:e0239787.

d) Deol ZK, Lakhanpal S, Franzon G, Pappas PJ. Effect of obesity on chronic venous insufficiency treatment outcomes. *J Vasc Surg Venous Lymphat Disord* 2020;8:617-28.e.

**2. Hormone replacement therapy impact on venous-lymphatic disease**

*Query used for the literature search*

(hormonal therapy) AND (vein)

(hormonal therapy) AND ((lymphedema) OR (lipedema))

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### Main findings

Sex hormones have an effect on both the vein and lymphatic wall and in their venous and lymph content, therefore potentially leading to inflammation, reflux, oedema and thrombosis. Despite the popular belief, strong evidence-based data on the real risk of contraception and substitution hormonal therapy on venous and lymphatic disease are still missing according to these authors search. Two studies suggest increased risk of venous thromboembolism in oral contraceptive users who were already affected by chronic venous disease. Nevertheless, several biases limit the value of this conclusion.<sup>404</sup> The hormonal role has been pointed out by a recent review showing how venous thromboembolism remains one of the leading causes of maternal mortality, with a pregnancy and postpartum thrombotic incidence that has not decreased over the past two decades.<sup>405</sup> Recent data suggest transdermal hormonal administration can reduce the venous thromboembolic risk in menopausal women. Yet, risk/benefit analysis should be always performed carefully for each and every specific case.<sup>406</sup> The effect of estrogen on the lymphatic vessel remain unexplored up to our knowledge, yet, in a parallelism with the hormonal role in the arterial and venous system, the same hormones variation could significantly influence edema formation and lymphatic function.<sup>407</sup> In a similar way, preliminary data suggest a hormonal role also in the lipedema pain context, yet without solid data defining the impact of an eventual hormonal therapy on the disease evolution. Further studies on this clinically impacting topic are encouraged.<sup>408</sup>

### Analyzed literature possible biases

Different drugs and regimens in heterogeneous populations.

### Suggested next research lines

Clinical and lab assessment of different hormonal protocols in homogeneous study populations.

### Related statement in layman's term for public vein-lymphatic awareness

Oral and injectable hormone use can increase the risk of venous thromboembolism. Transdermal administration can reduce the thromboembolic risk but more investigations are needed for a final recommendation.

### Suggested pertinent extra readings

a) Badreddine J, Lee MH, Mishra K, Pope R, Kim JY, Hong SH, *et al.* Continuing perioperative estrogen therapy

does not increase venous thromboembolic events in transgender patients: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2022;26:2511-7.

b) Kaemmler LM, Stadler A, Janka H, von Wolff M, Stute P. The impact of micronized progesterone on cardiovascular events - a systematic review. *Climacteric* 2022;25:327-36.

### 3. Supplements for venous-lymphatic disease patients

#### Query used for the literature search

(supplement) AND (venous)

(supplement) AND (lymphatic)

#### Main findings

The health market is flooded by nutritional supplements claiming benefits too often not properly demonstrated and moreover from products not properly validated. Differently from medications, supplements are regulated post-market with no regulatory body assessing the contents and safety before the selling to the consumer. The typical example is offered in the United States by the Dietary Supplement Health and Education Act for which the Food and Drug Administration consider the supplements as food. The Food and Drug administration gets involved in supplements only in case a supplement has already caused an health issue (<https://www.fda.gov/food/dietary-supplements>). The topic is of significant importance considering over 70% of the United States population take some supplement regularly and that potential serious side effects have been already reported.<sup>409</sup> Properly produced and tested nutrients with antioxidant properties have recently demonstrated potentials in improving ulcer healing. Among these ones, omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, probiotics and resveratrol. The benefit has been reported to be more evident in case of an initial deficiency. Nevertheless, because of several investigations biases, further studies are needed before recommending their use in the clinical practice.<sup>295</sup> Preliminary data are suggesting potential effects of an anti-oxidant, anti-bacterial and anti-inflammatory supplement (hydroxytyrosol) on lymphedema, but also in this case more robust literature is needed to counteract inappropriate prescriptions.<sup>410</sup> "Nutravigilance" is a term indicating "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects related to the use of a food, dietary supplement, or medical food": it is practice is of pivotal importance in all medical specialties and related scientific societies.<sup>411</sup>

*Analyzed literature possible biases*

Lack of properly conducted large studies on the different supplements.

*Suggested next research lines*

RCT including objective validated outcome measures.

*Related statement in layman's term for public vein-lymphatic awareness*

Up to the knowledge of this experts panel, no food, drink or supplement has scientifically demonstrated to improve venous-lymphatic circulation. Relying to the expert physician is of paramount importance before using whatever supplement.

*Suggested pertinent extra readings*

a) Raposo A, Saraiva A, Ramos F, Carrascosa C, Raheem D, Bárbara R, *et al.* The Role of Food Supplementation in Microcirculation-A Comprehensive Review. *Biology (Basel)* 2021;10:616.

b) Olas B, Urbańska K, Bryś M. Saponins as Modulators of the Blood Coagulation System and Perspectives Regarding Their Use in the Prevention of Venous Thromboembolic Incidents. *Molecules* 2020;25:5171.

c) Sato Y. [Study of Formulation Development Based on the Pharmacokinetic Properties of Functional Food Components]. *Yakugaku Zasshi* 2019;139:341-7. [Japanese].

d) Olas B. Dietary Supplements with Antiplatelet Activity: A Solution for Everyone? *Adv Nutr* 2018;9:51-7.

**4. Diet regimens for venous-lymphatic disease patients**

*Query used for the literature search*

(diet) AND ((venous) OR (lymphedema) OR (lipedema))

*Main findings*

Obesity is a recognized risk factor for lower limb venous disease,<sup>181</sup> while preliminary data are suggested that a low body mass index is associated with pelvic venous disorders.<sup>400</sup> In this context, body weight control by appropriate diet is of paramount importance, moreover considering that the inclusion of specific elements such as vitamin D and folic acid might even improve venous ulcer healing.<sup>412</sup> Moreover, diet-induced obesity was recently found associated with lymphedema development, suggesting the body weight impact on both the venous and lymphatic drainage.<sup>413</sup> Proper nutrition demonstrated a possible role also in thrombosis management, particularly in COVID-19 time.<sup>414</sup> Nevertheless, specific regimen diets have not been

compared head to head in homogenous study populations, limiting the possible recommendations on the topic. Empirically, a diet favoring proper hydration and low levels of oxidants could favor drainage fluidity and anti-inflammatory conditions, yet proper evidence is still needed and encouraged. Recent literature focused on a modified Mediterranean diet for favoring a body composition counteracting lipedema alterations and leading to an improvement in patients quality of life. Further investigations are needed also on this topic, focusing on specific nutritional regimens.<sup>415</sup>

*Analyzed literature possible biases*

Lack of investigations on standardized nutritional regimen for specific venous and lymphatic drainage impairment conditions.

*Suggested next research lines*

Single component diet variation in homogeneous study populations in terms of vein/lymphatic drainage compromise.

*Related statement in layman's term for public vein-lymphatic awareness*

Up to the knowledge of this experts panel, no specific diet has been scientifically validated for venous-lymphatic improvement. A diet aimed to avoid obesity, oxidative stress and excessive venous-lymphatic dilation should be preferred and customized on the specific subject case.

*Suggested pertinent extra readings*

a) Cooper ID, Crofts CAP, DiNicolantonio JJ, Malhotra A, Elliott B, Kyriakidou Y, *et al.* Relationships between hyperinsulinaemia, magnesium, vitamin D, thrombosis and COVID-19: rationale for clinical management. *Open Heart* 2020;7:e001356.

b) Barber GA, Weller CD, Gibson SJ. Effects and associations of nutrition in patients with venous leg ulcers: A systematic review. *J Adv Nurs* 2018;74:774-87.

c) Olas B. Dietary Supplements with Antiplatelet Activity: A Solution for Everyone? *Adv Nutr* 2018;9:51-7.

d) Morelli VM, Lijfering WM, Bos MH, Rosendaal FR, Cannegieter SC. Lipid levels and risk of venous thrombosis: results from the MEGA-study. *Eur J Epidemiol* 2017;32:669-81.

**5. Physical activity for venous-lymphatic disease patients**

*Query used for the literature search*

(physical activity) AND (chronic venous disease)  
(physical activity) AND (lymphedema)

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### Main findings

Activation of the lower limb muscle masses is pivotal for venous-lymphatic drainage. The same activation of the thoraco-abdominal pump can influence venous-lymphatic return. Appropriate physical exercise activity demonstrated potentials in both subjective<sup>416</sup> and objective measures of leg drainage. Physical activity demonstrated to be a meaningful addition to compression in lower limb lymphedema patients, even in advanced stage.<sup>417</sup> The need of an exercise regimen is included also in the latest indications for lipedema management.<sup>418</sup> Despite the potentials of physical exercise, the literature is still lacking properly collected data supporting the recommendation of a specific protocol for the different vein-lymphatic conditions and related stages. Future research should take into consideration standardization and reproducibility, in particular concerning intensity, frequency and time of the exercise. Sample size, blinding and disease severity homogeneity must also be taken into consideration.<sup>419</sup> Indeed, a recent publication focused on the importance of increasing adherence to methodological quality for physical activity report in order not to downgrade the results of available studies on the important topic of the physical exercise as health tool.<sup>420</sup>

### Analyzed literature possible biases

Lack of standardization and reproducibility in the assessed exercise types.

### Suggested next research lines

Validation of specific exercise protocols.

### Related statement in layman's term for public vein-lymphatic awareness

Physical activity requiring progressive, gentle activation of leg calf muscle can facilitate venous drainage. Physical activity requiring sudden activation of the calf muscle, possible leg constriction or trauma can harm venous drainage. A specialist consult can help identifying the correct exercise type.

### Suggested pertinent extra readings

a) Schmidt AC, Gomes LP, Marinelli CM, Gomes RZ. Effects of strengthening the surae triceps muscle on venous pump function in chronic venous insufficiency. *J Vasc Bras* 2021;20:e20200197.

b) Espeit L, Rimaud D, Le Mat F, Cudel C, Micol I, Bertoletti L, *et al.* Fatigue, physical activity and quality of life in people self-reporting symptoms of chronic

venous disease. *J Vasc Surg Venous Lymphat Disord* 2022;10:1147-1154.e1.

c) Kiloatar H, Aras O, Korkmaz M, *et al.* An evaluation of quality of life, physical activity level and symptoms in patients with early stages of chronic venous disease. *J Vasc Nurs* 2021;39:108-13.

d) Padberg FT Jr, Johnston MV, Sisto SA. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. *J Vasc Surg* 2004;39:79-87.

## 6. Graduated compression in occupational and sport settings

### Query used for the literature search

(compression stockings) AND (occupational)  
(compression stockings) AND (sport)

### Main findings

Occupational activities characterize by prolonged standing up or sitting can lead to swelling and discomfort also in subjects not affected by venous insufficiency. Certified graduated compression stockings have demonstrated to potentially counteract both the related oedema and symptomatology.<sup>421</sup> Large studies are needed to assess the possibility of reducing the risk of developing chronic venous insufficiency in this population, together with the cost-efficacy of an appropriate compression prescription.<sup>422</sup> A recent randomized comparative trial demonstrated how 18-21 mmHg graduated compression stockings might be effective in occupational swelling and symptomatology control, yet further studies are needed to compare the effect of different compression types (graduated *vs.* progressive) and doses.<sup>423</sup> Further investigations are needed also to define the objective benefit brought by certified graduated compression into the sport world. Heterogeneous outcomes have been reported on the topic also by the most recent reviews, with data showing no benefit<sup>424</sup> while others demonstrated a positive impact on muscle performance and symptomatology.<sup>425</sup> Specific research was done also on not athletic subjects reporting potential benefit of graduated compression on exercise performance also in this kind of population.<sup>426</sup> A strong focus on the type of compression used and of related physical activity should be developed in order to avoid reviewing data coming from too heterogeneous settings.

### Analyzed literature possible biases

- Lack of standardization of «long standing up workers» definition.

- Heterogeneous sport activity and related compression type and dose.

*Suggested next research lines*

- Multicenter occupational studies in homogeneous study populations.
- Specific sport activities data review and implementation.

*Related statement in layman's term for public vein-lymphatic awareness*

Certified properly prescribed graduated compression can improve perceived exertion after walking and subjective comfort after prolonged sitting. Prescription by a health-professional is recommended.

*Suggested pertinent extra readings*

a) Guedes PM, Saldanha NA, Matos PM, Carvalho FS, Veiga G, Norton P. Occupational leg edema-use of compression stockings. *Porto Biomed J* 2020;5:e093.

b) Al Bimani SA, Gates LS, Warner M, Bowen C. Factors influencing return to play following conservatively treated ankle sprain: a systematic review. *Phys Sportsmed* 2019;47:31-46.

c) Won YH, Ko MH, Kim DH. Intermittent pneumatic compression for prolonged standing workers with leg edema and pain. *Medicine (Baltimore)* 2021;100:e26639.

d) Gianesini S, Raffetto JD, Mosti G, Maietti E, Sibilla MG, Zamboni P, *et al.* Volume control of the lower limb with graduated compression during different muscle pump activation conditions and the relation to limb circumference variation. *J Vasc Surg Venous Lymphat Disord* 2020;8:814-20.

**7. Graduated compression during prolonged travels**

*Query used for the literature search*

(graduated compression) AND (travel)

*Main findings*

Air travel longer than 4 hours has been recently confirmed to be a risk factor for venous thrombo-embolism, increasing proportionally with the same travel time. Patients with pre-existing venous disease and or other thrombotic risk factors might benefit from certified graduated compression use.<sup>427</sup> The air travel is associate with an increased thromboembolism risk not only for the prolonged sitting position, but also for the pressurized cabin atmosphere characteristics leading to possible traveler hypoxia and dehydration.<sup>428</sup> A recent review dem-

onstrated that also after just 3 hours a benefit in edema and thrombotic risk management can be observed following the use of proper graduated compression. While high quality evidence supported the advantage in edema control, low quality data supported the compression use for thrombo-prophylaxis. Further studies are needed to clarify the objective benefit.<sup>429</sup> Frequently, the topic of the long-travel potential impact on the venous system is contextualized only in the airline sector. Nevertheless, recent literature has brought attention to the possible impact also of long road travels and future investigations on the topic are encouraged to clarify the role of the sitting position versus the locomotion type.<sup>430</sup> Future investigations on long distance travel effects on venous-lymphatic circulation should be as standardized as possible in the data collection and includes same patients re-assessment considering the vast majority of investigations on this field enrolled the study population for only one trip, moreover with the assessment performed in different timings.<sup>431</sup>

*Analyzed literature possible biases*

Heterogenous timing in data collection.

*Suggested next research lines*

Multicenter data collection on homogenous study populations traveling not only by plane.

*Related statement in layman's term for public vein-lymphatic awareness*

Certified properly prescribed graduated compression stockings can reduce leg swelling after 4 hours flight. Patients at risk of venous-thromboembolism should wear certified compression stockings prescribed by an expert health-professional.

*Suggested pertinent extra readings*

a) Clarke MJ, Broderick C, Hopewell S, Juszczak E, Eisinga A. Compression stockings for preventing deep vein thrombosis in airline passengers. *Cochrane Database Syst Rev* 2021;4:CD004002.

b) Sachdeva A, Dalton M, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* 2018;11:CD001484.

**8. Neuromuscular electrical stimulation evidence in venous-lymphatic disease management**

*Query used for the literature search*

(electrical stimulation) AND (calf)

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### Main findings

The medical market is offering several neuro-electrical stimulation devices aimed to improve venous drainage and decrease the thrombotic risk. Among these devices, too many are not validated by proper scientific investigations. A 2017 Cochrane analysis concluded that neuro-electrical stimulation showed no significant benefit in venous thrombo-prophylaxis compared to the traditional methods, but might bring some advantage versus no prophylaxis. Data in support of this statement are of low medium quality, therefore further investigations have been recommended.<sup>432</sup> Different modalities of electrical stimulation are available and unidirectional high voltage pulsed current type demonstrated superiority in wounds healing.<sup>433</sup> A recent randomized comparative trial involving 76 chronic venous disease patients, showed electrical stimulation benefits on femoral vein Time Averaged Mean Velocity, on Aberdeen Varicose Veins Questionnaire Score and on Venous Clinical Severity Score.<sup>434</sup> Similar data were reported in an observational study in the same year, using the device for 4-6 hours per day, for 6 weeks.<sup>435</sup> Future multi-center investigations should focus on specific different protocols and devices, while addressing also the minimum required time to obtain an effect, considering a multiple hours per day use could limit the patient compliance.

### Analyzed literature possible biases

Devices and protocols heterogeneity.

### Suggested next research lines

Multicenter different protocols and devices testing.

### Related statement in layman's term for public vein-lymphatic awareness

Neuromuscular electrical stimulation has shown preliminary evidence of potential benefit in leg venous drainage. More data are needed to validate its use, for which an indication of the expert physician is suggested.

### Suggested pertinent extra readings

a) Palmieri B, Vadalà M, Laurino C. Electromedical devices in wound healing management: a narrative review. *J Wound Care* 2020;29:408-18.

b) Vena D, Rubianto J, Popovic MR, Fernie GR, Yaddollahi A. The Effect of Electrical Stimulation of the Calf Muscle on Leg Fluid Accumulation over a Long Period of Sitting. *Sci Rep* 2017;7:6055.

## 9. Aquatic activity evidence in venous-lymphatic disease management

### Query used for the literature search

((hydrotherapy) OR (balneotherapy)) AND ((venous) OR (lymphatic))

### Main findings

The potential benefit brought by aquatic immersion for lower limb venous-lymphatic disorders have been known since the ancient times. The physical, thermal and chemical properties of the aquatic environment can all be involved in this process, yet proper data collection is needed to move from empiricism toward evidence-based science. This concept has been clearly underlined by two recent reviews focusing on the venous and on the lymphatic context, respectively. In particular, for the venous aspects, moderate- to low-certainty evidence showed balneotherapy may result in a moderate improvement in pain, quality of life and skin pigmentation, while no clear effect on disease severity signs and symptoms score, adverse effects, leg ulcers and oedema were reported.<sup>436</sup> The analysis focusing on the lymphatic system showed the lack of clear evidence favoring aquatic vs. land-based exercises, yet with a clear lack of properly performed investigations on lower limb lymphedema.<sup>437</sup> A standardized and reproducible protocol of aquatic exercise for lower limb venous-lymphatic patients was presented in 2017, demonstrating benefits in lower limb volume, symptomatology and ankle range of motion improvement.<sup>438</sup> The same exercise protocol was tested inside and outside the aquatic environment, demonstrating the advantage of the water immersion context.<sup>439</sup> Another recent randomized trial showed the benefit of balneotherapy in advanced chronic venous disease patients in terms of clinical status improvement and quality of life, pointing out the rapidly occurring benefit within the 3 months of activity initiation, with a slower improvement rate from 3 months to 2 years.<sup>440</sup> Further investigations are needed to standardize at best the type of aquatic activity favoring the most the venous and/or lymphatic system, based also on the different disease stages.

### Analyzed literature possible biases

Lack of standardization in the aquatic protocols.

### Suggested next research lines

Multicenter trials involving the same standardized protocol.

### Related statement in layman's term for public vein-lymphatic awareness

Specifically standardized aquatic exercises demonstrated to be beneficial for leg venous-lymphatic drainage. SPA/



aquatic not specific walks are still needing proper scientific validation.

*Suggested pertinent extra readings*

a) Thibert A, Briche N, Vernizeau BD, Mougin-Guillaume F, Béliard S; Therapeutic Patient Education Working Group of the French Society of Vascular Medicine. Systematic review of adapted physical activity and therapeutic education of patients with chronic venous disease. *J Vasc Surg Venous Lymphat Disord* 2022;10:1385-400.

b) Stier-Jarmer M, Throner V, Kirschnack M, Frisch D, Schuh A. [Effects of Kneipp Therapy: A Systematic Review of Current Scientific Evidence (2000-2019)]. *Complement Med Res* 2021;28(2):146-59. [German].

c) Badtieva VA, Trukhacheva NV, Savin EA. [The modern trends in the treatment and prevention of lymphedema of the lower extremities]. *Vopr Kurortol Fizioter Lech Fiz Kult* 2018;95:54-61. [Russian].

d) Carpentier PH, Satger B. Randomized trial of balneotherapy associated with patient education in patients with advanced chronic venous insufficiency. *J Vasc Surg* 2009;49:163-70.

**10. False claims on lifestyle for potential venous-lymphatic benefit**

*Query used for the literature search*

(life-style) AND ((venous) OR (lymphatic)); (false claims) AND ((venous) OR (lymphatic)) (disinformation) AND ((venous) OR (lymphatic))

*Main findings*

Health misinformation can be defined as a “health-related claim that is based on anecdotal evidence, false, or misleading owing to the lack of existing scientific knowledge” and it has been representing an exponentially growing issue in the digital and social network era.<sup>441</sup> Lower limb venous and lymphatic disease is affected by this “infodemic” phenomenon, with many potentially false claims also regarding the related life-style, such as high-heel use, crossing leg habit, sun and warm exposure, and so much more. Concerning the high-heel use, preliminary evidence suggest a potential impairment of the venous valvular-calf pump function indeed. Yet, more studies are needed for a final recommendation on the exact shoe type and disease stage contraindication.<sup>442</sup> Crossing legs demonstrated showed an impact on arterial share stress, but data are still needed regarding venous hemodynamics.<sup>443</sup> A not excessive sun exposure actually demonstrated a possible protective role against venous thromboembolism,<sup>444</sup> while im-

**12. LIFE-STYLE, SPORT, NUTRITION**



Life-style, sport & nutrition can all be considered like drugs: harmful or helpful based on how they are practiced. Evidence-based statements on the related venous-lymphatic field are reported. Insights available here: [www.vwinfoundation.com/fake-news-free-project/](http://www.vwinfoundation.com/fake-news-free-project/)

**LIFE-STYLE, SPORT, NUTRITION**

1. Obesity, postural defects, physical inactivity are risk factors for leg chronic venous disease.
2. Oral and injectable hormone use can increase the risk of venous thromboembolism. Transdermal administration can reduce the thrombo-embolic risk but more investigations are needed for a final recommendation.
3. Up to the knowledge of this experts panel, no food, drink or supplement has scientifically demonstrated to improve venous-lymphatic circulation. Relying to the expert physician is of paramount importance before using whatever supplement.
4. Up to the knowledge of this experts panel, no specific diet has been scientifically validated for venous-lymphatic improvement. A diet aimed to avoid obesity, oxidative stress and excessive venous-lymphatic dilation should be preferred and customized on the specific subject case.
5. Physical activity requiring progressive, gentle activation of leg calf muscle can facilitate venous drainage. Physical activity requiring sudden activation of the calf muscle, possible leg constriction or trauma can harm venous drainage. A specialist consult can help identifying the correct exercise type.
6. Certified properly prescribed graduated compression can improve perceived exertion after walking and subjective comfort after prolonged sitting. Prescription by a health-professional is recommended.
7. Certified properly prescribed graduated compression stockings can reduce leg swelling after 4 hours flight. Patients at risk of venous-thromboembolism should wear certified compression stockings prescribed by an expert health-professional.
8. Neuromuscular electrical stimulation has shown preliminary evidence of potential benefit in leg venous drainage. More data are needed to validate its use, for which an indication of the expert physician is suggested.
9. Specifically standardized aquatic exercises demonstrated to be beneficial for leg venous-lymphatic drainage. SPA/aquatic not specific walks are still needing proper scientific validation.
10. Medical information is heavily subjected to fake news: relying always on validated scientific papers and experts health professionals is crucial.

\*Not for profit educational initiative  
-WIN foundation, ONUS



\*Nutritional part developed in collaboration with the Italian Association of Dietology & Clinical Nutrition

Figure 12.—Public vein-lymphatic awareness evidence-based statements in layman’s terms regarding life-style, sport and nutrition for vein-lymphatic patients.

mersion in hot water confirmed the venous dilation, but actually showed an increase in the flow velocity.<sup>445</sup> A recent investigation identified seven modifiable independent predictors of lower limb varicosities development: frequent lifting of heavy objects, drinking <5 cups of water/day, infrequent/no consumption of fiber-rich food, standing more than 4 h/day, irregular defecation habit, sleeping less than 8 h/day, and smoking.<sup>446</sup> All these data needs further larger investigations before coming to a strong recommendation in terms of life-style and, so far, not much has changed from the Edinburgh Vein Study showing no consistent relationship with any lifestyle factor.<sup>447</sup> It is the hope of the all the authors of the present work that this document will stimulate colleagues from all around the world to keep moving from not validated claims to scientific facts, from empiricism to evidence based data (Figure 12).

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*Analyzed literature possible biases*

Lack of multicenter analysis on false claims and life-style topics for venous-lymphatic disease management.

*Suggested next research lines*

Detection of the most common false claims and evidence based analysis.

*Related statement in layman's term for public vein-lymphatic awareness*

Medical information is heavily subjected to fake news: relying always on validated scientific papers and experts health professionals is crucial.

*Suggested pertinent extra readings*

- a) Ogoh S, Nagaoka R, Mizuno T, Kimura S, Shidahara Y, Ishii T, *et al.* Acute vascular effects of carbonated warm water lower leg immersion in healthy young adults. *Physiol Rep* 2016;4:e13046.
- b) Soot LC, Moneta GL, Edwards JM. Vascular surgery and the Internet: a poor source of patient-oriented information. *J Vasc Surg* 1999;30:84-91.

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1. Schmidt AL, Zollo F, Del Vicario M, Bessi A, Scala A, Caldarelli G, *et al.* Anatomy of news consumption on Facebook. *Proc Natl Acad Sci USA* 2017;114:3035-9.
2. Waszak P, Kasprzycka-Waszak W, Kubanek A. The spread of medical fake news in social media - The pilot quantitative study. *Health Policy Technol* 2018;7:115-8.
3. Brashier NM, Schacter DL. Aging in an Era of Fake News. *Curr Dir Psychol Sci* 2020;29:316-23.
4. Naeem SB, Bhatti R, Khan A. An exploration of how fake news is taking over social media and putting public health at risk. *Health Info Libr J* 2021;38:143-9.
5. Wang Y, McKee M, Torbica A, Stuckler D. Systematic Literature Review on the Spread of Health-related Misinformation on Social Media. *Soc Sci Med* 2019;240:112552.
6. Carrion-Alvarez D, Tijerina-Salina PX. Fake news in COVID-19: A perspective. *Health Promot Perspect* 2020;10:290-1.
7. Gianesini S, Obi A, Onida S, Baccellieri D, Bissacco D, Borsuk D, *et al.* Global guidelines trends and controversies in lower limb venous and lymphatic disease: narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics, 23-25 January 2019. *Phlebology* 2019;34(Suppl):4-66.
8. Alsaigh T, Fukaya E. Varicose Veins and Chronic Venous Disease. *Cardiol Clin* 2021;39:567-81.
9. Dua A, Desai SS, Heller JA. The Impact of Race on Advanced Chronic Venous Insufficiency. *Ann Vasc Surg* 2016;34:152-6.
10. Salim S, Machin M, Patterson BO, Onida S, Davies AH. Global Epidemiology of Chronic Venous Disease: A Systematic Review With Pooled Prevalence Analysis. *Ann Surg* 2021;274:971-6.
11. Moffatt C, Keeley V, Quere I. The Concept of Chronic Edema-A Neglected Public Health Issue and an International Response: the LIM-PRINT Study. *Lymphat Res Biol* 2019;17:121-6.

12. Mortimer PS. Evaluation of lymphatic function: abnormal lymph drainage in venous disease. *Int Angiol* 1995;14(Suppl 1):32-5.
13. Partsch H, Lee B. Phlebology and lymphology—a family affair. *Phlebology* 2014;29:645-7.
14. Scherer K, Khilnani N. Evaluation and Management of Patients with Leg Swelling: Therapeutic Options for Venous Disease and Lymphedema. *Semin Intervent Radiol* 2021;38:189-93.
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*Conflicts of interest.*—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

*Authors' contributions.*—All authors read and approved the final version of the manuscript.

*Acknowledgements.*—We would like to deeply thank all the Scientific Societies and Institutions who officially endorsed this initiative, together with all the non-health professionals who took part in the verification of the document parts in layman's terms dedicated to public vein-lymphatic awareness: American Vein & Lymphatic Society; American Venous Forum; Argentina College of Vascular and Lymphatic Surgery; Asian Venous Forum; Association of Brazilian Phlebo-Lymphology; Association of Vascular Surgeons of Ukraine; Australian & New Zeland Phlebology Society; Austrian Society of Phlebology; Balkan Venous Forum; Baltic Society of Phlebology; Bangladesh Vascular Society; Benelux Association of Phlebology; Bolivian Society of Phlebology; Bulgarian Society of Vascular Surgery; Canadian Society of Phlebology; Central America Vascular Surgery Society; Chile Foundation of Phlebology & Lymphology; Chile Phlebo-Lymphology Society; Chinese Society of Phlebology (CINA); Colombian Vascular Surgery Association; Costa Rica Peripheral Vascular Surgery Society; Czech Society of Phlebology; Dominican Society of Vascular Surgery; Dubai Health Authority; Egypt Africa Venous Lymphatic Association; Egyptian Venous Forum; El Salvador Vascular Surgery Society; French Society of Phlebology; Georgian Association of Vascular Surgery; Hellenic Society of Phlebology; Hungarian Venous Forum; Indonesia Venous Forum; International Compression Club; International Society of Lymphology; International Union of Angiology; International Vascular Endovascular Research Consortium; Italian Association of Dietology and Clinical Nutrition; Italian Association of Phlebology; Italian Chapter of the International Society of Lymphology; Italian National Federation of Medical Boards; Italian Society of Clinical and Experimental Phlebology; Italian Society of Phlebo-Lymphology; Japanese Society of Phlebology; Kazakh Society of Phlebology; Latin America Venous Forum; Mexican Academy of Phlebo-Lymphology; Mexican Society of Vascular Surgery; Mexican Venous Forum; National College of Phlebology Russia; Near East North Africa venous-lymphatic forum; Paraguay Association of Phlebo-Lymphology; Perú Society of Phlebo-Lymphology; Phlebo-lymphology Spanish Chapter; Polish Society of Phlebology; Portuguese Society of Vascular Surgery; Romanian Society of Phlebology; Russian Phlebology Association; Saint Petersburg Venous Forum; Serbian College of Phlebology; Sociedad Panamericana de Flebología y Linfología; Society for Vascular of Singapore; South Africa Lymphatic & Venous Society; Surgical College J. Raymond Tournay; Swiss Society of Phlebology; Thai Society of Phlebology; Thai Vascular Association; Turkish Society of Phlebology; Uruguay Society of Phlebology & Lymphology; Vascular Surgery Society of Egypt; Venous Association of India; World Union of Wound Healing.

*History.*—Article first published online: March 17, 2023. - Manuscript accepted: February 28, 2023. - Manuscript received: February 21, 2023.

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