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Refining diagnosis and management of chronic venous disease: Outcomes of a modified Delphi consensus process

Teresa Lucia Aloi[a,*], Giuseppe Camporese[b], Marcello Izzo[c,d], Dimitris Kontothanassis[e], Angelo Santoliquido[f]

[a] Istituti Clinici Scientifici Maugeri IRCCS, Cardio-Angiology Unit of Montescano and Pavia Institute, Italy
[b] Unit of Angiology, Department of Cardiac, Thoracic, and Vascular Sciences, Padua University Hospital, Padua, Italy.
[c] Math Tech Med Medicine & Bioscience - Research Center- University of Ferrara-, Italy
[d] Compression Therapy Study Group (CTG)-, Italy
[e] Istituto Flebologico Italiano, Ferrara, Italy
[f] Catholic University of Sacred Heart, Gemelli Policlinic Foundation - IRCCS, Rome, Italy

A B S T R A C T

Chronic venous disease (CVD) is a common condition with major health consequences that is associated with poor long-term prognosis, significant socioeconomic impact, disabling symptoms and reduced quality of life. To provide practical guidance for diagnosis and management of CVD, a Delphi panel of 5 experts in steering committee and 28 angiologists/vascular surgeons met with the major aim of providing a supplement for established national and international guidelines. A total of 24 statements were voted upon in two rounds, of which consensus was reached on 22 statements, indicating a high level of overall agreement. Consensus was reached on 7 of 8 statements relative to diagnosis (CEAP classification, diagnostic tools, QoL assessment, diagnostic imaging) and on 15 of 16 statements on management (conservative treatments, compressive therapy, pharmacological therapy, surgical treatment). The results of the consensus reached are discussed herein from which it is clear that diagnostic and management approaches utilising personalised therapies tailored to the individual patient should be favoured. While it is clear that additional studies are needed on many aspects of diagnosis and management of CVD, the present Delphi survey provides some key recommendations for clinicians treating CVD that may be useful in daily practice.

Introduction

Chronic venous disease (CVD) is a problem of major health importance. CVD is generally defined as any morphological or functional abnormality of long duration that affects the venous system, with manifest symptoms and/or signs of disease warranting both investigation and eventual treatment [1]. Valve failure in the lower extremities, allowing retrograde flow of blood, leads to a variety of pathologies, which are not limited to pain, oedema and skin changes [2]. As is well known, CVD has both serious and life-threatening consequences, and, unfortunately, poor long-term prognosis [1,3].

There are several well-established risk factors for development of CVD that include increasing age, female sex, obesity, previous pregnancy and multiparity, positive family history, constipation and environmental/occupational factors that require standing for long periods of time [4,5]. CVD is a common condition, with a reported prevalence from 5% and 30% in the adult population [6–8]. Prevalence rates for varicose veins are much higher, reaching up to 73% in women and 56% in males [6]. The prevalence of all categories of CVD increase with age, while the more serious consequences of CVD, such as venous ulcers, have an estimated prevalence of 1–2%, increasing to at least 4% in the population over 80 years of age [9]. Due to limitations in function, CVD restricts the ability to engage in social and occupational activities, thereby reducing the overall quality of life, imposing financial constraints and early retirement in over 10% of workers [10].

Treatments for CVD are grouped into conservative and interventional therapies [1,11]. The former comprise a wide variety of strategies including lifestyle modification, pharmacological treatment, compressive leg garments, wound and skin care, and exercise therapy. Four groups of venoactive pharmacological therapies have been studied: coumarins, flavonoids, saponosides and other plant extracts [1]. Glycosaminoglycans (GAGs) as such as sulodexide and mesoglycan may also be useful treatment options, but require additional evidence of efficacy. Numerous invasive options are available for more advanced stages of disease [1]. These include sclerotherapy, endovenous ablation, endovenous deep system therapy and surgical management. Surgical options include surgery for truncal vein or venous tributaries, perforator vein surgery and valve reconstruction [1,11].

Depending on wound size and duration, from 30% to 75% of patients with venous leg ulcers will experience healing within 6 months of

* Corresponding author at: Istituti Clinici Scientifici Maugeri IRCCS, via Maugeri 4, 27100 Pavia, Italy.
E-mail address: teresa.aloi@icsmaugeri.it (T.L. Aloi).

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treatment [12]. Wound Healing Society guidelines attest that wounds that fail to decrease in size during the first month of treatment are unlikely to heal; as such, these wounds would likely benefit from advanced therapies and referral to a wound care specialist [13].

At present, there are Accreditation Council for Graduate Medical Education–accredited fellowships that specifically focus on wound management, and expertise in wound healing may be found in a variety of specialties such as vascular medicine and surgery, podiatry and dermatology. Moreover, despite the availability of well-established national and international guidelines for venous ulcer management, recommendations typically focus on treatment of a diseased population [3,14–17]. As such, greater guidance relevant for daily practice is needed for the individual patient for both diagnosis and treatment [18].

To aid clinicians with practical guidance for diagnosis and management of CVD, a Delphi panel of 5 experts in steering committee and 28 angiologists/vascular surgeons met with the objective of favouring appropriate and personalised diagnosis and to provide direction for appropriate conservative therapy, compressive therapy, venoactive drugs, other pharmacological therapy and indications for surgical approaches which are in line with current international recommendations. The results of the Delphi consensus meeting are summarised herein.

Materials and methods

Delphi process and steering committee.

The Delphi process is a well-accepted and widely adopted technique to obtain consensus from experts. The method uses successive iterations in a survey type format, wherein in each round of voting the participants assess the results and feedback, and subsequently modify a statement or recommendation until broad consensus is reached [19]. The Delphi approach combines the principles of evidence-based medicine supported by systematic literature reviews with an iterative and anonymous voting process. Use of this process overcomes problems associated with group dynamics in decision-making committees as the experts can provide their opinions freely, individually and anonymously [20]. Furthermore, the Delphi method is a rapid and economically-favourable means of interacting with a large group of experts.

A classic Delphi process begins with an exploratory questionnaire containing mainly open-ended response questions in which to develop subsequent questionnaires [21,22]. A modified two stage Delphi technique, which omits the qualitative round, can be employed in those situations where the statements are derived from the literature and if the main aim is to take the determine current opinion on a specified topic [23–25]. Herein, the traditional round 1 that begins with an open-ended questionnaire was replaced with a predefined list of statements selected by the authors after a comprehensive literature review to identify best practice evidence on how to screen, diagnose and treat patients with CVD. While there is no fixed number of rounds in a Delphi survey [26], other similar studies have suggested consensus can be reached after two rounds [27–31].

The Steering Committee was composed of 5 experts (TLA, GC, MI, DK, AS), who oversaw formulation of 24 statements that were divided into the main areas of diagnosis and management. Steering Committee members were identified by several criteria including their recognised expertise and/or academic rank, publications, attendance at national meetings and participation in clinical trials. A questionnaire was developed considering national and international guidelines, published evidence and clinical experience. Towards this end, a comprehensive literature review was performed to identify relevant publications from 1980 to 2018, and the Medline database was searched for English-language literature. The search strategy combined headings and keywords for “management of chronic venous insufficiency”, “management of chronic venous disease”, “post-thrombotic syndrome”, “compression therapy”, “graduated compression elastic stockings” and “quality of life assessment for venous disease”. Each member of the panel was assigned a group of statements, screen the literature, and eliminate the irrelevant papers. When given the initial list, all the members of the panel collectively choose the final list of statements to be administered to the panellists. All relevant studies were later rated using the same approach used by the Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) on management of Chronic Venous Disease; the grading system of the European Society of Cardiology was used [16].

An expert panel consisting of 28 angiologists/vascular surgeons from across Italy (Appendix 1) was invited to participate in the Delphi process. Panellists were invited by the steering committee to participate on the basis of their interest and expertise in the management of patients with CVD, and were selected from different angiology/vascular surgery units (hospital or university based) and experience in angiology/vascular surgery. The experts were identified from all geographic regions of Italy to include all Italian areas/regions as to be representative of clinical practice in the field of CVD management in Italy. The entire Delphi process took place over a period of 8 months. The process used herein was composed of three steps: (i) establishment of a scientific steering committee of 5 experts who reviewed the relevant literature and developed the statements to be ranked; (ii) first round of online statement voting by the expert panel; (iii) final consensus meeting in which the expert panel and Steering Committee discussed the results of the online consensus survey followed by another round of voting for statements with partial consensus or negative consensus.

The panellists were asked to anonymously express their level of agreement with each statement, using a 5-point Likert scale (1 = disagree; 2 = somewhat disagree; 3 = neither agree nor disagree; 4 = somewhat agree; 5 = agree). The use of a 5-point Likert Scale with this consensus threshold was defined a priori as described in previous studies with this modified process [29,31–34]. Consensus was considered if either the sum of answers 1 and 2 (negative agreement), or 4 and 5 (positive agreement) exceeded 70%, as described in previous studies with this method [29,32,33,35]. The results are expressed as a percentage of agreement or disagreement with each statement.

Results

Overall process.

Following compilation of the results of the first online survey, consensus (≥70% either positive or negative) was reached on 12 of 24 statements. The 12 statements for which consensus was not achieved in the first round were discussed, modified and then voted on again. The final voting results are shown in Table 1. Consensus (agreement/disagreement) was reached on 22 of the 24 statements, indicating a high level of overall unanimity on diagnosis and management.

Statements on diagnosis.

The 8 statements on diagnosis were divided into 4 subareas: CEAP classification, diagnostic tools, quality of life (QoL) assessment and diagnostic imaging. Consensus agreement/disagreement was reached for all 5 statements on CEAP classification. For diagnostic tools, no consensus reached on statement 6 about the need to integrate diagnostic evaluation with the Venous Severity Scoring (VSS) and clinical exam scores for CVI. Consensus agreement/disagreement was reached for the statements on QoL and diagnostic imaging.

Statements on management.

The 16 statements on management of CVD were divided into 4 subareas: conservative treatments, compressive therapy, pharmacological therapy and surgical treatment. Consensus agreement/disagreement was reached for all the statements in each subarea with the exception of the statement regarding best elastic compression in symptomatic C1 patients.

Table 1
Results of Delphi consensus statements on CVD.

MAIN AREAS		Statement	Consensus agreement	Level of evidence**	References
Diagnosis	CEAP classification	1. Chronic venous disease (CVD) represents the initial phases of disease (CEAP C0-C2), while chronic venous insufficiency (CVI) represents the more advanced stages (CEAP C3-C6).	85% agreement	B	[17,36–39]
		2. CVD should always be classified as symptomatic or asymptomatic independently of the stage of disease.	86% agreement	B	[36–39]
		3. Patients classified as CEAP C2 have the same clinical characteristics.	92% disagreement	D	
		4. CEAP is not sufficient for diagnosis of post-thrombotic syndrome (PTS).	74% agreement	D	
		5. Skin changes are typical of the advanced CEAP stages (C4-C6).	79% agreement	C	[45,46]
	Diagnostic tools	**6. For CVI, clinical-diagnostic assessment should be integrated with VCSS and clinical exam.**	No consensus	B	[16,48]
	QoL assessment	**7. Evaluation of the efficacy of treatment for symptomatic CVD requires the use of generic (e.g. SF36 and EQ-5D) and specific questionnaires (such as CIVIQ 14 for mild/moderate cases and VEINES QoL in more severe cases before and after treatment).**	75% agreement	B	[49–53]
	Diagnostic imaging	**8. Diagnosis of PTS should be made only with Doppler echography.**	96% disagreement	D	
Management	Conservative treatments	**9. Treatment of symptomatic CVD (CEAP C0-C2) is continuous.** *	96% agreement	D	
		10. Identification of polymorphisms that may affect the progression of CVD may be useful to orient the clinician towards earlier and more intense therapy.	74% agreement	D	
		11. Treatment of CVI (apart from its aetiology) is continuous. *	96% agreement	C	[56,57,60,61]
		12. There is no recognised pharmacological treatment available for secondary prevention of superficial venous thrombosis.	89% disagreement	D	
		13. The best medical treatment in symptomatic C0-C1 patients is venoactive drugs + elastic compression + lifestyle modification (weight control, physical activity, dietary intervention)	85% agreement	C	[56]
	Compressive therapy	**14. The best elastic compression treatment in symptomatic C0-C1 patients is compressive therapeutic stockings certified as a medical device (RAL-GZ classification).**	No consensus	D	
		15. Patients classified as CEAP C3 (oedema) should always be treated with an elastic bandage in the acute phase and with elastic compression via with certified therapeutic stockings (RAL-GZ classification) in the maintenance phase, and guided by the ABI (Ankle/Brachial Index).	78% agreement	C	[56]
		16. Compressive therapy (RAL-GZ class ≥II) is indicated as prophylaxis in patients with PTS.	85% agreement	B	[66–70]
		17. The optimal duration of compressive therapy following surgical intervention is not standardised.	82% agreement	D	
	Pharmacological therapy	**18. The best pharmacological treatment in symptomatic C0-C1 patients is with drugs with anti-inflammatory and endothelial repair activity.**	88% agreement	C	[71–73]
		19. In choosing a venoactive drug, agents that act on the pathogenetic mechanisms of CVD should be preferred.	82% agreement	C	[74–77]
		20. There is currently no scientific evidence regarding the efficacy of dietary integrators in treatment of CVD.	79% agreement	D	
	Surgical treatment	21. Surgical therapy should be minimally-invasive.	82% agreement	C	[16,81]
		22. The saphenic axis should be surgically preserved if the varicose disease is limited to the saphenous tributaries.	96% agreement	C	[15,16]
		23. Laser thermoablation (1470 nm) or radiofrequency should be mainly applied to treatment of the saphenic vein axis.	89% agreement	A	[16,81–83]
		24. Pharmacological prophylaxis for thrombosis is always indicated following venous surgery in patients with moderate to high risk.	89% agreement	B	[84]

* Statement modified during plenary discussion. Bold Statements indicate those for which consensus was not achieved during the first round of voting.
** Levels of evidence A: data derived from multiple randomised clinical trials or meta-analyses [15].
Levels of evidence B: data derived from a single randomised clinical trial or large non-randomised studies. [15]
Levels of evidence C: consensus of opinion of the expert and/or small studies, retrospective studies, registries.[15]
Levels of evidence D : lack of scientific evidence.

Discussion

A high level of consensus was reached on 22 of the 24 statements proposed on diagnosis and management of CVD. This is significant as the major aim of the present Delphi consensus committee was to provide clinicians with greater guidance in daily practice in evaluating and treating patients with CVD. The present statements on CVD can thus help serve to supplement established national and international guidelines.

Diagnosis.

CEAP classification.

It is clear from statements 1 and 2 that stages C0–2 represent the initial phases of disease, while C3–6 should be considered as more advanced stages. Moreover, CVD should always be classified as either symptomatic or asymptomatic. Consensus for statement 2 was reached during plenary discussion, where it was highlighted that quantification of symptoms is a fundamental aspect in assessing patients with CVD. This is a valid consideration even when bearing in mind that early intervention may have the possibility to slow progression of disease. In this light, correlation between venous symptoms and the presence of telangiectases and/or reticular veins remains a highly controversial topic in CVD [36]. It is thus important to distinguish venous symptoms from those of other causes, which may not be specific for CVD. Indeed, the use of common language and terminology has been proposed to help in investigation and management of CVD [37]. While obvious signs are hallmarks of CVD, such as varicose veins and venous ulcers, other symptoms such as heaviness, swelling, muscle cramps, restless legs and pain are less specific [38,39]. Moreover, evaluation of symptoms is also of fundamental importance as an indicator of efficacy of therapy.

There was broad disagreement on statement 3, indicating that the vast majority of specialists feel that C2 patients do not have the same clinical characteristics. In this regard, it should be kept in mind that CEAP classification is not a classification of severity, and the C2 subcategory comprises all types of varicose veins [40]. In fact, among C2 patients, there is a variety of risk factors and age, accounting for some variability [41]. In addition, ultrastructural morphology of venous valves in chronic venous disorders may not depend on age in patients with C2 disease [41]. It has also been demonstrated that there is a high degree of histological variability in patients with C2 disease with marked inflammation in some patients, which may help explain the different severity of symptoms among patients even with the same stage of disease [40,41]. Taken together, these considerations confirm that C2 is a subgroup that encompasses a wide variety of clinical characteristics and symptoms.

The specialists reached agreement for statement 4, advocating that CEAP classification is not sufficient for diagnosis of post-thrombotic syndrome (PTS). Indeed, at present there is no gold standard laboratory, imaging or functional test that firmly establishes its diagnosis [42]. In patients with objectively confirmed prior DVT who have typical PTS symptoms and signs, PTS is usually the correct diagnosis, but may occur at ~6 months after acute DVT [43]. Alternative classification schemes such as the Villalta scale may be more useful, which takes account both patient-reported symptoms and objective clinical assessment. In fact, the Villalta Scale has been recommended as a standard to define PTS for use in clinical investigations by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (SSC-ISTH) [44].

In line with statement 5, skin changes can be considered as typical in advanced stages of CVD (C4–6). Early studies showed that the severity of microangiopathy in patients with chronic venous insufficiency determines the extent of trophic disturbances of the skin [45]. In the initial phases of skin changes, pigmentation is attributable to melanin, although the mechanisms responsible have remained unclear [46]. Persistent inflammatory state with matrix metalloproteinase and cytokine expression has been related to tissue damage and degradation, resulting in both skin changes and venous leg ulcer [46]. Moreover, older age is related to a greater number of insufficient venous segments and increased probability of clinical progression of CVD from varicose veins to CVI (C(3)-C(6), trophic skin changes and venous ulcers [47].

Diagnostic tools.

No consensus was reached about the need to integrate diagnostic evaluation with the Venous Clinical Severity Score (VCSS) and clinical exam scores in CVI. Indeed, current recommendations provide descriptions of different diagnostic tools, but no specific guidance on which to use and when, only stating that in diagnostic work-up the nature of the problem and severity of the disease should be determined [16]. In addition, it should be kept in mind that the VCSS was designed to complement the CEAP system and not as a standalone tool. Indeed, the VCSS is often considered as an adjunct to venous outcome assessment [48].

Evaluation of QoL.

It is well-established from multiple studies that QoL is progressively impaired in CVD/CVI, involving primarily physical items and emotional role, with worsening of mental items only in advanced stages [49,50]. Improvement of health-related QoL is a main therapeutic goal in chronic CVD, and the specialists held that QoL requires detailed evaluation before, during and after treatment. The specialists wholly agreed that QoL evaluation should be performed using both specific and generic questionnaires to assess the impact of treatment on QoL and integrated with clinical scores (e.g. CEAP, VCSS) [51]. For example, generic questionnaires such as Short-Form-36 (SF-36), Short-Form-12 (SF-12) and EuroQol 5 Dimension (EQ-5D) can measure overall well-being without specific reference to CVD. However, more specific questionnaires may also be considered such as the thoroughly validated instruments CIVIQ and VEINES-QOL, although factorial stability has not been demonstrated for the latter [52]. The scale measures symptoms, limitations and psychological impact over the past four weeks. VEINES-QOL was designed as a self-assessment tool that contains 26 items under two dimensions to measure QoL and symptoms. Lastly, QoL measurement can also be used to assess the effectiveness of therapeutic devices such as elastic stockings [53].

Diagnostic imaging.

For the last statement (#8) on diagnostic imaging tools in CVD, there was near unanimous disagreement that diagnosis of PTS should be made only with Doppler ultrasound. As mentioned, there is no recognised gold standard laboratory, imaging or functional test that establishes diagnosis of PTS. Indeed, the Villalta scale currently remains the gold standard for the diagnosis of PTS, as recommended by SSC-ISTH [44]. However, ultrasound remains the most useful test for diagnosis of recurrent deep vein thrombosis [54,55].

Management.

Conservative therapy.

According to consensus reached on statement 9, treatment of CVD should be continuous. Indeed, symptom-based treatment of CVD is now widely advocated. When considering the most appropriate treatment option for CVD, clinicians should consider both objective signs and subjective symptoms of disease. Moreover, in line with the objectives of the steering committee on individualised treatment, treatment decisions should be made on a case-by-case basis. These concepts are also in full agreement with another recent consensus statement advocating the greater need for symptom-based treatment of CVD [56]. Similarly, the experts wholly agreed on the need for continuous treatment of CVI (statement 11).

In further agreement with advocating a more individualised approach to management of CVD, the specialists also found consensus on statement 10 regarding the utility of identifying genetic polymorphisms that may affect progression of CVD. Indeed, several polymorphisms have been identified that appear to stratify with disease, notably HFE p.C282Y as well as those in metalloproteases [57–60]. Other researchers have proposed that a genetic risk score might be useful in distinguishing patients at risk for more severe disease [61]. Even if the

therapeutic implications of the presence of at-risk polymorphisms are limited at present, the experts felt that an individual harbouring an at-risk polymorphism might help to orient the clinician towards earlier and more intense therapy.

Near complete disagreement was reached for statement 12, suggesting that there may be valid and recognised pharmacological treatment available for secondary prevention of superficial venous thrombosis. While the experts agreed that there are no recognised guidelines for superficial venous thrombosis, several treatments are available as secondary prevention, and other approaches can be considered as valid, including surgery and elastic compression [62]. In considering pharmacological treatments, the randomised METRO study was mentioned by the experts in which mesoglycan oral tablet is being compared to placebo for secondary prevention of superficial venous thrombosis (NCT03428711). The primary outcome measure of METRO is cumulative recurrence of thrombosis, with cumulative occurrence of distal events, symptoms (measured with the revised VCSS) and QoL measured with VEINES)-QOL/Sym scores as secondary outcomes. Recruitment in the study is ongoing.

Agreement was reached for the statement (#13) that the best medical treatment in symptomatic C0-C1 patients is venoactive drugs + elastic compression + lifestyle modification (weight control, physical activity, dietary intervention). These interventions are fully supported by clinical evidence [56]. In symptomatic CVD, the experts agreed that choice of therapy should be based on individual factors. In this light, invasive procedures, compression therapy and pharmacological treatment should all be considered as complementary, and not as competing. Indeed, patients may often prefer less invasive over more aggressive management strategies. Given that combination therapy has been shown to have additive effects, combining various methods is thus a valid therapeutic strategy [56].

Compressive therapy.

No consensus was reached for statement 14 regarding best elastic compression treatment in symptomatic C0-C1 patients. There was ample discussion that while compression therapy may have few effects on microcirculation, its effects on macrocirculation are more evident, reducing perivascular inflammation [63]. This is important as inflammatory processes are involved in structural remodelling in venous valves and the vein wall, which lead to valvular incompetence and development of varicose veins [63]. Considering this, it seems reasonable to speculate that therapeutic, and not preventive, compressive treatment may reduce the risk of CVD progression if applied when first symptoms appear [64]. The use of graded elastic compressive stockings (between 18 and 46 mmHg of tension) is a mainstay in the treatment of CVI [1]. Treatment with a 23 to 46 mmHg compression stocking seems to result in significant improvement in pain, swelling, skin pigmentation, activity and well-being if compliance of 70% to 80% is achieved [65]. A UIP consensus document suggests that the risk of developing venous symptoms is increased in women, advanced age and obesity, and that the use of 10–15 mmHg compression provides benefit in those with symptoms related with CEAP class 0 and 1 [36]. Indeed, treatment should be based on physical advice, elastic compression, venoactive drugs, sclerotherapy, correction of foot static disorders and reduction of body weight. Notwithstanding, the therapeutic approach should also be guided by the clinician's experience and patient preferences. The lack of consensus on this statement was largely correlated to the fact that the evidence base mostly involves patients in stages more advanced than C0-C1. There was also agreement on statement 15 regarding the use of an elastic bandage in the acute phase in C3 patients, followed by compressive therapy with stockings in the maintenance phase and guided by the ABI.

Compressive therapy (RAL-GZ class ≥II) was advocated by the experts in treatment of post-thrombotic syndrome (statement 16). The use of compression therapy for post-thrombotic syndrome has been well-established in several studies [66,67]. The application of a high compression class elastic knee-high (3rd class - 34/46 mmHg of ankle compression) 2–3 weeks after the acute event has been shown to reduce the incidence of symptomatic proximal-vein thrombosis by 57% [66]. This has been confirmed in a randomised trial in 180 patients followed for 5 years in which support stockings of 30–40 mmHg of ankle compression were used [67]. These recommendations are in spite of the controversial SOX study in which elastic compression stockings did not prevent PTS after a first proximal DVT [68]. However, guidelines support the use of compressive stockings for prevention of PTS, as well as for prevention of ulcers, and largely supported by a recent Cochrane review [69]. The experts also noted that the AHA has modified their recommendations, stating that the effects of elastic compression are uncertain and indicated only in case of oedema after a thrombotic event [70].

Regarding the last statement (# 17) on compressive therapy, its duration was held by experts to be variable, and not standardised, following surgery for varicose veins. This expert agreement further advocates an individualised approach to treatment [56].

Pharmacological therapy.

Consensus was reached on all 3 statements in the subarea on pharmacological treatments. For statement 18, best pharmacological treatment in symptomatic C0-C1 patients was held to be drugs with anti-inflammatory and endothelial repair activity. Indeed, drugs can attenuate various elements of the inflammatory cascade, particularly leukocyte-endothelium interactions which are fundamental in many aspects of the disease, should be preferred whenever possible [71]. Biochemical, immunohistochemical and functional studies have all indicated that the vein wall and valve are involved in the primary events leading to venous disease [72]. Inflammatory cells have a central role in the pathophysiology of CVD and venous leg ulcers. In addition, considering the pathogenesis of CVD, and in particular the relationship between haemodynamics, venous hypertension and inflammation, an increase in venous pressure with consequent alteration of shear stress can modify the valve walls, thereby favouring venous reflux and inducing a state of chronic inflammation [72,73]. The experts agreed that it is important to intervene on these mechanisms, especially in the initial stages of disease. It has also been demonstrated that the increase in hydrostatic pressure and parietal tension causes the activation of MMP, with modification of endothelial function and smooth muscle cells [72]. All these observations support the use of agents in CVD with an endothelial target.

Regarding statement 19 in choice of venoactive drugs, it was held that agents that act on the pathogenetic mechanisms of CVD should be preferred. In this light, mesoglycan, a natural glycosaminoglycan preparation, was mentioned as a preferred agent attenuates proliferation of vascular smooth muscle cells through activation of AMP-activated protein kinase and mTOR [74]. Another potential benefit of mesoglycan is that the compound has been shown to decrease capillary permeability, enhancing systemic fibrinolysis and preventing clinical formation of venous thrombus [75]. As such, mesoglycan may have beneficial effects on vascular proliferative disorders. In CVD, mesoglycan has shown benefit improving in microvascular function after 3 months of treatment in C1-C4 women [76]. In a randomised clinical trial vs placebo, in addition to established venous ulcer therapy, mesoglycan was associated with significantly faster and more frequent ulcer healing, with no safety concerns [77]. The available evidence would appear to suggest that mesoglycan may have a protective effect in patients with venous thrombosis, supporting its use in patients with chronic venous insufficiency and persistent venous ulcers, in association with compression therapy and elastic compression stockings [78]. As already mentioned, the randomised, placebo-controlled METRO study (NCT03428711) is ongoing in which mesoglycan is being studied in secondary prevention of superficial venous thrombosis.

In the last statement in this subarea (#20), the experts fully agreed that the evidence for use of dietary integrators is insufficient. In this regard, rutosides were mentioned as some data has shown encouraging results in treatment of CVD and PTS, although there is little solid

evidence of efficacy [79]. A recent Cochrane review concluded that there is no evidence that rutosides are superior to placebo or elastic compression stockings [80].

Surgical treatment.

Consensus agreement was reached for all four statements on surgical treatment of CVD. In line with current guidelines and clinical evidence, when indicated surgery should preferably be minimally-invasive (statement 21) [16,81]. For treatment of incompetent great saphenous vein, endovenous thermal ablation rather than high ligation and inversion stripping of the saphenous vein to the level of the knee is recommended (statement 22) [15,16]. Guidelines from the NHS are also in favour of minimally-invasive techniques for treatment of varicose veins, and a Cochrane review confirmed that ultrasound-guided foam sclerotherapy, radiofrequency ablation and endovenous laser therapy are at least as effective as surgery in the treatment of great saphenous varicose veins [82,83]. Lastly, NICE guidelines recommend that endovenous treatment should constitute the first treatment of choice for people with confirmed varicose veins and truncal reflux [83].

Laser thermoablation (1470 nm) or radiofrequency have their main application in treatment of the saphenic vein axis (statement 23) [16,81,83]. Finally, pharmacological prophylaxis for thrombosis is always indicated following venous surgery in patients with moderate to high risk, also due to favourable cost considerations (statement 24) [84].

Conclusions

The present Delphi consensus on CVD was conceived with the objective of aiding clinicians by providing practical guidance for diagnosis and management of CVD. Moreover, approaches favouring appropriate and personalised diagnosis were discussed in order to provide broad indications for conservative therapy, compressive therapy, venoactive drugs, other pharmacological therapy and surgical approaches. It was not our attempt to substitute international and national recommendations, but rather to complement them with a series of consensus statement that can orient diagnosis and treatment. Broad consensus was reached on 22 of the 24 statements formulated, which should help guide greater personalisation during management of CVD that takes into account the current evidence base. There are some limitations to the present consensus. These include the fact that the panel was composed of experts only from Italy, which could limit the possibility of generalising the consensus reached. This could be addressed by involving a broader panellist board that would promote discussion on these important issues with the medical community. While further studies are needed on many aspects of CVD, the present Delphi survey provides some key recommendations for clinicians treating CVD that may be useful in routine practice.

Conflict of interests

The authors declare no conflicts of interest.

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Mediolanum Farmaceutici had no involvement in the Delphi consensus process or in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the article for publication.

Appendix A. APPENDIX 1

Specialists participating in the study: Corrado Amato, Giovanni Ambrosino, Vincenzo Aversano, Biagio Bonfiglio, Eugenio Bucherini, Edoardo Cervi, Maurizio Ceschin, Leonardo Chiodi, Giuseppe Corsi, Aldo Crespi, Michelangelo Di Salvo, Edoardo Esposito, Roberto Fadani, Elias Fares Estephan, Filippo Ferrara, Marco Filipponi, Martinlla Fullone, Maria Rosa Angela Gaiani, Enrico Leo, Stefano Mancini, Stefano Molfetta, Francesco Monteleone, Manlio Prior, Tonino Proia, Stefania Puddu, Franco Ribero, Stefano Spiezia, and Antonio Trani.

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