Management of Varicose Veins and Chronic Venous Insufficiency in a Comparative Registry with Nine Venoactive Products in Comparison with Stockings

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Abstract

The aim of this registry study was to compare products used to control symptoms of CVI. Endpoints of the study were microcirculation, effects on volume changes, and symptoms (analogue scale). Pycnogenol, venoruton, troxerutin, the complex diosmin-hesperidin, Antistax, Mirtoselect (bilberry), escin, and the combination Venoruton-Pycnogenol (VE-PY) were compared with compressions.

No safety or tolerability problems were observed. At inclusion, measurements in the groups were comparable: 1,051 patients completed the registry. *Best performers*: Venoruton, Pycnogenol, and the combination VE-PY produced the best effects on skin flux. These products and the combination VE-PY better improved PO_2 and PCO_2. The edema score was decreased more effectively with the combination and with Pycnogenol. Venoruton; Antistax also had good results. Considering volumetry, the best performers were the combination PY-VE and the two single products Venoruton and Pycnogenol. Antistax results for edema were also good. The best improvement in symptoms score were obtained with Pycnogenol and compression. A larger decrease in oxidative stress was observed with Pycnogenol, Venoruton, and with the VE-PY combination. Good effects of Antistax were also observed. Parestesias were lower with Pycnogenol and with Antistax. Considering the need for interventions, the best performers were Pycnogenol, VE-PY, and compression. The efficacy of Pycnogenol and the combination are competitive with stockings that do not have the same tolerability in warmer climates. A larger and more prolonged evaluation is suggested to evaluate cost-efficacy (and non-interference with drugs) of these products in the management of CVI. The registry is in progress; other products are in evaluation.

Keywords

- chronic venous insufficiency
- venous disease
- varicose veins
- elastic stockings
- venoactive compounds
- edema

Venous disease, varicose veins, and chronic venous insufficiency (CVI) are very common clinical conditions associated with impaired venous circulation causing discomfort, edema, and skin changes.[1,2] Causes of CVI are untreated venous disease and varicose veins, consequences of deep venous thrombosis (DVT), and conditions resulting in venous hypertension, alterations in venous competence, and venous valve disruption (as seen after DVT).[1,2] The diagnosis of CVI is mainly clinical and is defined by ultrasound.[1–3] Main managements and treatments are compression, surgical and interventional treatments (including sclerotherapy), and skin and wound care if indicated.[3] CVI is socially very relevant as it affects some 5% of patients in the United States. According to a recent consensus,[4] the management of CVI is based on limb elevation, compression, topical treatments, and skin management and interventions (surgery or sclerotherapy).

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Several drugs and non-prescription products are also available and may be used to improve signs and symptoms of CVI as supplementary treatment. These compounds—including prescription products and products considered nutritional or pharmaceutical-standard (PS) supplements—are available for supportive management of CVI in its evolution. Compression and stockings cannot be used in all patients, all the time, and it is very difficult to use elastic stockings in summer or in hot climates and warmer countries.

In this registry study, 10 supplementary managements (including nine products) were used for supportive, symptomatic management of CVI.[5] Self-medication and individual management are concepts in great expansion, particularly interesting in this context as PS supplements (all these products can be considered PS supplements) represent ideal solutions for self-medication, for most patients considering their accessibility without prescription (with a single initial indication by physicians). The safety of these products is optimal even when other concomitant drugs are used (i.e., antihypertensives.) to treat clinical conditions or control risk conditions (i.e., statins).

Main endpoints of this registry study were objective changes in microcirculation and limb volume (assessed by volumetry) and clinical CVI symptoms assessed on a visual analogue scale.

The aim of this registry study was a comparative evaluation of products (used as a single medication) in controlling signs and symptoms of CVI.

Patients and Methods

The registry included patients with CVI and signs/symptoms (CEAP grades 3–4a; moderate to severe clinical symptoms).[1–4]

Otherwise healthy patients, using no other drugs, without diabetes or metabolic disorders were included. The patients were characterized by varicose veins, present for > 5 years, ankle swelling, partially relieved by leg elevation, no orthopedic problems, and body mass index (BMI) < 27. All these patients had chosen to opt, temporarily, for personal reasons, for conservative treatments for at least 1 year, and had temporarily requested conservative management. Most patients were on a waiting list for sclerotherapy or minimal surgery. CVI was defined as indicated in previous classifications (*Haimovici's Vascular Surgery*, 3). All included patients (in all groups) were equally characterized by varicose veins, perimalleolar edema, initial skin changes and discoloration (without present or previous ulcerations), symptoms (heavy legs after standing), minimal paresthesias,[4] and by ultrasound indicating in all "registry" limbs, superficial reflux. Hemodynamic (increased ambulatory venous pressure) parameters were defined according to previous publications and as defined by the recent international consensus.[4] All products were used at the suggested or recommended dosage. The duration of the observational, open, registry period was of at least 12 months.

Brief description of the products: the composition and characteristics of most products in this field are often not detailed. Some products do not specify the dosages or the rationale for its use in the compositions.[5] All products are considered as safe. Venoruton (Paroven in U.K.) (Novartis) has been present in the market for decades. It is very safe; one study reports the use of Venoruton for 5 years without side effects in CVI. Venoruton improves peripheral edema in CVI and diabetic microangiopathy, decreasing their progression. Pycnogenol (Horphag)[6–12] can be considered a "model" product as per several recent studies. It improves CVI and affects oxidative stress with a mild antiaggregating and, possibly, an antithrombotic activity. This specific extract can be used as a supplement in symptomatic varicose veins and in CVI. Pycnogenol[6–12] well evaluated in technical studies, has shown a significant effect even at low dosages (100 mg/d); it improves (CVI-related edema) comparatively more and better than other compounds.[11] Supplementation is effective in microcirculatory disorders with a specific activity on peripheral edema (even during long flights) and equally in venous and diabetic microangiopathy.

Table 1 The nine venoactive products used in the study

	Dosage	Doses per day
Venoruton (Novartis)	1,500 mg	0-(β-hydroxyethyl)-rutosides
Pycnogenol (Horphag)	150 mg	French Maritime Pine bark extract
Troxerutin	1,000 mg	several preparations available
Diosmin + hesperidin		diosmin mg 450 flavonoids (esperidine = mg 50)
Antistax (Boehringer Ing)	750 mg	*360 mg extract red grape leaf*
Mirtaven (*Mirtoselect*) Indena	600 mg	*Mirtoselect* (*standardized bilberry extract* with 36% anthocyanins)
Troxerutin generic	800 mg	troxerutin 300 mg
ESSAVEN-Escin (Aventis-Sanofi, generic)	100 g dry extract of horse chestnut	Triterpene glycosides (triterpene 22.5%)
Ve-Pycno (Novartis and Horphag; noncombined preparation)	150 + 1,500 mg	*Supercompound*

The brand Troxerutin (produced by five international producers) is used at the dosage of some 600 to 1,000 mg/d and is found in several generic preparations. The product has been available for years, but studies have been fragmentary and often limited. Troxerutin is generally effective for the treatment of the pre-varicose and varicose syndrome, as a supplementary management in varicose ulcers, in controlling symptoms of thrombophlebitis, postthrombotic conditions, and hemorrhoids. Troxerutin has also been used to control muscle pain and edema.

The complex diosmin + hesperidin (90% diosmin and 10% other flavonoids expressed as hesperidin) has also been widely studied; it appears to be less powerful and effective than Venoruton and Pycnogenol in CVI patients (considering edema, microcirculation, and the most common signs/symptoms). It is definitely less potent than Pycnogenol alone (to obtain comparable results, i.e., on edema). It needs a dosage some 10 times higher than Pycnogenol.

Antistax (Boehringer-Ingelheim, Germany; tablets 360 mg) has red grape leaf extracts (GLE) as active ingredients.[13–16] It is a single specific preparation. It is used at a dosage of some 700 to 1,000 mg/d. Signs/symptoms are positively affected. CVI-related edema is less affected; progression studies in CVI need to be completed and, possibly, dosage studies may evaluate higher dosages.

Mirtoselect (used at the dosage of some 600 mg/d) is a proprietary product (Indena, Milan, Italy) extracted from bilberry. The venous circulation of the retina is a specific target application for this products that also has a significant activity on peripheral venous microcirculation and on edema in CVI. A specific combination (Mirtogenol, including Mirtoselect + Pycnogenol) has been mainly developed for retinal and eye microcirculatory problems, but it also has a significant efficacy in venous insufficiency and CVI-related microcirculatory alterations.

Non-branded, generic troxerutin (used at doses around 800 mg/d) is available as various generic products, broadly comparable to branded Troxerutin.

Oral escin (used at the dose of some 600 mg) has been used in several preparations. The product is derived from horse chestnut. The main product (Essaven, Aventis) includes an alcoholic extract of horse chestnut, triterpenic glycosides and escin + sutin. The exact composition (including 50 mg of the active component escin) is not completely clear. Three capsules daily are generally used for patients with CVI. Dosages are not well defined for the different degrees of CVI.

A supplement association Venoruton-Pycnogenol (VE-PY) 1,500 mg + 150 mg/d has been evaluated recently (using the two separate compounds). The combination product improves the efficacy of the single products without side effects. There is a very significant effect on CVI-derived edema. The cost of this combination is, however, relatively high.

Compression

"Standard management" for CVI was considered compression[1,3,4] to be associated with surgical or interventional methods when indicated. A group of comparable patients with CVI was monitored to evaluate effects and tolerability of only elastic stockings on CVI in the same period of time. In the reference or "standard" management group, below-knee elastic stockings (Sigvaris, Winterthur, Switzerland; with compression at the ankle of 20–25 mm Hg) were used daily during standing and the working activities and removed only for bed rest.

Ultrasound evaluation was performed according to defined standard.[3,4,17–21] The *registry* was based on objective and subjective technical measurements useful to quantify CVI by monitoring the clinical attributes specific of CVI.[4,22–24]

The *microcirculation* was non-invasively evaluated (standard room temperature of 22°C) at the internal perimalleolar region using a laser Doppler flowmeter (Laserflo, Vasamedics, St. Paul, Minnesota, United States). The *resting flux* (in flux units) was measured (as a continuous measurement over 1 minute of recording, after 3 minutes of stabilization). *Transcutaneous PO_2 and PCO_2* were measured at the distal, internal perimalleolar region with a Kontron Combi Sensor (Kontron Instruments, U.K.) after 20 minutes of heating of the probe at 40°C.[22]

Edema. The *rate of ankle swelling* (in mL/min/100 cc of tissue) was measured with a straingauge plethysmograph (Hokanson SPG16, St. Paul, Minnesota, United States). The patient was resting supine for 10 minutes and then asked to stand. A straingauge had been applied at the lower ankle circumference at the nonsupporting limb, with the patient holding onto a frame and supporting his/her weight on the opposite leg. The tangent to the 10th minute was considered proportional to capillary filtration.[18,20]

Volume. The volume evaluation was measured in a Plexiglas chamber including the knee and the leg (5 cm proximal to the distal edge of the rotula). The first volumetric evaluation was defined as 100% and the following variations were measured as a percent change. *Ankle circumference* was self-measured (in cm) with a tape, in the morning at 8 AM, at the minimal ankle circumference. All measurements, standards and reproducibility values, for these tests have been established in several previous studies and described in details in previous publications.[10–14]

The *clinical attributes* linked to CVI are shown in ►**Table 2**. The attributes were rated on a visual, analogue scale line from 0 (none/absent) to 5 (severe). At inclusion, all registry patients were between the moderate and severe level. No previous DVT or post-thrombotic syndrome had been recorded or documented or detected at inclusion. Duplex ultrasound indicated that the deep venous system was patent and that there was no significant obstruction with a predominant venous incompetence at superficial level.

Previous surgery and/or sclerotherapy were performed (but not in all patients and limbs) at least 1 year before the start of the registry.

Common complications due to CVI (possible hemorrhage or thrombotic complications of the varices and possible skin alterations and ulcerations) were evaluated during the observation period. *Oxidative stress* was evaluated—in peripheral venous blood—in a random (20%) subgroup of patients for each management group.[25]

Limb thermography was performed to evaluate possible, localized, superficial thromboses or inflammatory conditions

Table 2 Summary table: base, inclusion data

Groups	Microcirculation model			Edema score	Symptoms	Oxidative stress	10 Paresthesia (number)	Score 0–5
	R-FLUX	PO_2	PCO_2		Score 0–5			
1. VENOR	2.82	51	31	4.2	3.9	388	78/83	3.7
SD	0.1	4	3.2	1.1	0.8	22		0.9
2. PYC	2.7	52	30	3.9	4	378	98/122	3.8
SD	0.11	3.2	2.4	0.7	1	23		0.5
3. TROX	2.8	53	29	4.1	3.9	398	70/77	3.7
SD	0.2	2.4	3	0.8	0.3	18		0.6
4. D-E	2.82	52	29	4.2	4	382	65/71	3.6
SD	0.1	2.2	2.1	0.3	0.7	31		1
5. ANX	2.8	51	28	4.1	3.8	379	67/73	3.7
SD	0.11	2.1	2	0.8	0.9	24		1.1
6. MYRT	2.76	52	30	4.0	3.9	388	70/77	3.5
SD	0.1	2.6	2.5	0.7	0.8	12		1
7. FLEB	2,82	53	29	3.9	3.7	378	68/74	3.6
SD	0.2	3.2	3	0.8	0.7	22		0.8
8. ESC	2.78	52	31	4.1	4	382	55/64	3.7
SD	0.13	2.6	2.2	1	0.8	26		0.9
9. VE-PY	2.76	52	29	4.06	4.1	375	155/173	3.6
SD	0.1	3	2.5	1.1	0.4	22		0.5
10. ECOM	2.81	51	30	4.1	3.9	387	198/237	3.8
SD	0.2	2.1	2	0.5	0.7	21		1.1

Abbreviation: VE-PY, Pycnogenol + Venoruton association.
Note: All patients were treated/supplemented according to suggested dosages for at least 12 months.
Laser Doppler flux at the internal perimalleolar region; flux expressed in flux units; PO_2 and PCO_2: in mmHg.
The clinical picture included symptomatic varicose veins and CVI.
This study lasted at least four seasons for all patients. These are the initial, inclusional values.
Comparative standard management with elastic compression stockings is also shown.
Measurements include SD (however, all these items should be considered nonparametric: intra-individual variation in measurements is $< 8\%$).

(Flir, 440, Sweden). The possible presence of DVT was also evaluated (by ultrasound and D-dimer).

Supplement registry studies[26–29] are aimed to define the field of activity of supplements and possible preventive, preferably nonclinical applications that can be associated with self-management. They are planned and organized with the full attention and participation of the evaluation patients.

Commercial sponsorship from the producers of the tested supplement was not available. Safety and tolerability were assessed by weekly phone calls and mail contacts and laboratory measurements. Adverse experiences were evaluated throughout the registry and communicated to the monitors as soon as possible by SMS. All clinical adverse experiences were evaluated in terms of intensity: mild, moderate, or severe, and also considering duration, seriousness, outcome, and relationship to the registry. A diary recorded the use of any drug prescribed by the patient's physician according to needs. Treatments and other management costs or disease-related costs (including work disruptions, consultations, tests and hospital admissions) occurring during the registry period were also recorded by the registry patients.

Registry monitoring is regularly used to evaluate the clinical meaning of individualized medicine in specific patients.[24,25] The treatment/supplementation is monitored with a registry to assess its efficacy on different individuals and evaluate how different dosages and therapeutic schemes may affect different groups of patients (i.e., diabetics).

Statistical Analysis

All results were analyzed in comparison with the results from the SM (elastic compression stockings) considered as a baseline. Intra- and intergroup comparisons were performed by nonparametric tests and the ANOVA (analysis of variance) test, as appropriate. All target measurement values cannot be considered as normally distributed.

A p value < 0.05 was considered statistically significant. According to previous studies, comparable CVI groups of at least 30 patients were considered adequate to define a difference in target outcomes of at least 6 months.

Results

Safety

No safety or tolerability problems were observed in the study patients. All these products were fond to be very safe. No side effect was observed. Dropouts were caused by pure logistical problems and difficulties to follow instructions suggested for the follow-up.

►**Table 2** shows all the most important observed, target measurements at inclusion. Measurements in the 10 groups were comparable. The 10 groups were also comparable for age and sex distribution (►**Table 3**). A total of 1,051 patients completed the study with minimal variations. The measurements and the evaluations were made considering the most affected limb. All patients had CVI at both limbs with a significant asymmetry in signs, particularly edema (having only small varicose veins) in 184 patients. A global analysis indicated that all products were active with a prevalence on symptoms/signs or on the microcirculatory model.

Best Performers

Venoruton and Pycnogenol and the combination VE-PY produced the best effects on *resting flux* (RF, increased in these patients at the perimalleolar region). Perimalleolar flux was decreased by more than 44% with the combination, 38% with Venoruton, and 43% in the Pycnogenol group ($p < 0.05$ in comparison with the other groups). Elastic compression was significantly less effective (22% reduction in RF; $p < 0.05$). Also Pycnogenol, Venoruton, and the combination VE-PY improved $> 11\%$ *transcutaneous* PO_2 ($p < 0.05$, better, in comparison with all the other groups) and better than compression (8%). The same trend was observed with PCO_2 that decreased more in the Venoruton group (−9%) and with Pycnogenol (−10%) and with the combination VE-PY group (−10%) with 8% decrease in the reference compression group (difference not significant; ns). The *edema score* was decreased significantly more than in the other groups with the combination (−2.4) and with Pycnogenol (−2.2; $p < 0.05$) versus a −2.3 average with compression

Table 3 Results of all patients treated per suggested dosages for at least 12 months

Group	Numb (drops)	Age sex F = females	Micro-circulation model	PO_2	PCO_2	Edema score	Volume	Symptoms	Complications	Skin discoloration	Oxidative stress
			Resting flux (RF)				mL	Score 0–5	SVT		Difference
1.VENR	83 (4)	47; 3.2	−38%	+11%	−9%	−1.5	−103	−3.9	0/83	3/83	−31%
		33 F									
2.PYCNO	122 (5)	46; 2.6	−43%	+13%	−10%	−2.2	−107	−4.3	0/122	1/122	−39%
		58 F									
3.TROXER	77 (7)	48.2; 2,1	−22%	+5%	−5%	−1.1	−17	−1.9	2/77	2/77	−7%
		34 F									
4.DIO-ES	71 (11)	46.8; 2	−9%	+5%	−3%	−0.6	−33	−1.1	4/71	7/71	−4%
		33 F									
5.ANTX	73 (8)	47; 3.1	−5%	+5%	−4%	−1.5	−86	−1.1	4/73	11/73	−28%
		36 F									
6.MYRT	77 (6)	47.5; 2	−6%	+8%	-6%	−0.5	−43	−1.3	5/74	6/77	−9%
		38 F									
7.TRXER2	74 (7)	48.4; 2.2	−5%	+5%	−5%	−0.2	−34	−1.4	4/74	5/74	−12%
		37 F									
8.ESCIN	64 (7)	47; 3.1	−7%	+7%	−7%	−0.9	−46	−2	3/64	6/64	−11%
		37 F									
9.VE-PY	173 (12)	47; 3,2	−44%	+14%	−10%	−2.4	−112	−4.6	0/173	3/173	−41%
		88 F									
10.ECOMP	237 (18)	47.5; 3	−22%	+8%	−8%	−2.3	−117	−3.3	8/237	26/237	−2%
		166 F									
Total	1,051										

Abbreviation: SVT, superficial venous thrombosis.
Note: Clinical conditions: Varicose veins and CVI. Length: Management lasted at least four seasons.
Comparative standard management (group 10): elastic compression (stockings).
Best results underlined ($p < 0.05$ in comparison with other groups).

(value not significant in comparison with the previous two groups). Venoruton and Antistax also had good results.

Considering *volumetry*, the best performers were the combination Pycnogenol + Venoruton (difference >100 mL; $p < 0.05$) with a comparable decrease in volume with compression (ns difference) and the two single products Venoruton and Pycnogenol (groups 1 and 2). Antistax results for edema were also good with a decrease of 86 mL in volume.

The best decreases in *symptoms scores* were obtained with Pycnogenol and elastic compression (decrease > 4; $p < 0.05$) with a good result for Venoruton (−3.9; $p < 0.05$, in comparison with the other groups) and with compression (producing a decrease of 3.3 in score).

Occurring complications of CVI (minor or very minor superficial thrombotic episodes) are shown in ►**Table 3**. Venoruton, Pycnogenol, and the combination had a zero *complication rate*. However, more cases should be evaluated for this type of evaluation. Also, these managements (groups 1, 2, 9, and 10) had a significant lower rate of *skin discolorations* (within the follow-up period) due to the effects of CVI. Finally, a larger decrease ($p < 0.05$) in *oxidative stress* was observed (> 30%) in the Venoruton, Pycnogenol, and in the VE-PY combination groups (−41%) with no effects observable with elastic compression (−2%). A good effect of Antistax (−28%) was also observed.

►**Table 4** shows some accessory observations. *Thermal imaging* (showing an increase in skin temperature due to inflammation or presence of even minimal superficial inflammations or clots) indicated that the best performer was Pycnogenol ($p < 0.05$) (there were less hyperthermic areas during the follow-up). The *rate of DVTs* (documented by ultrasound + D-dimer) was limited; DVT was positive in a small number of cases and the differences cannot be considered conclusive.

Paresthesias were lower with Pycnogenol (4.1%) and Antistax (6.1%) ($p < 0.05$), both considering the number of patients with the symptom and the analogue score. The combination product was associated with 6.9% of patients with the symptoms and elastic compression to 29% of patients with symptoms.

Patients *with positive results*: the best results were obtained with the combination (Venoruton + Pycnogenol), with elastic compression and Pycnogenol (> 70% of patients with positive results) ($p < 0.05$).

Finally, considering the *need for interventional treatment* (sclerotherapy or surgery), the best performer can be considered Pycnogenol (only 11% of patients were in need of intervention) and the combination Venoruton + Pycnogenol (12%). With elastic compression 22% of the patients needed or required interventions. Venoruton was also effective as only 14% required or were considered in need of interventions (in all other groups the need was > 15%).

The combination VE-PY and Pycnogenol resulted – globally - the best supplementary, medical management considering all measurements, outperforming elastic compression. The tolerability for elastic stockings, particularly in warmer months (~5 mo/y), tends to be lower in warmer climates.

Discussion

This registry indicates that patients using supplementary medical management for CVI have benefits from several products. Pycnogenol supplementation and the combination Venoruton + Pycnogenol appear to have the most significant benefits on the microcirculation and on the most common[1–3] complaints and symptoms associated with CVI.

The best fields of application for supplements[30] are self-medication[31] or preclinical, borderline applications or the supplementary management of some risk conditions. Supplements—unless there are specific claims—are not generally used for treatment of signs/symptoms or clinical conditions. Supplement studies produce additional data to be compared with "background" historical data (based on the best available management) or to other management plans (i.e., the best or standard management). In this study, supplements were used according to the following rules:

Table 4 Results: other observational items

Group	Thermal changes	DVT	Paresthesia numbness	Score 0–5	Number of patients with positive results (%)	Need for interventional treatments (%)
1	33/83		18/83	2.11	55	14
2	24/122		7/122	1.2	73	12
3	31/77		9/77	2	34	18
4	44/71	1	25/71	3.4	22	26
5	54/71	1	5/73	1.3	21	26
6	29/77		22/77	2.7	24	28
7	29/74	1	23/74	3.3	21	31
8	33/64		20/64	2.3	26	22
9	12/173		12/173	1.1	78	11
10	46/237	1	69/237	2.1	77	22

Abbreviation: DVT, deep venous thrombosis.
Note: Pycnogenol and the VE-PY combination resulted as the best management in all measurements columns.

1. The use of the supplement was suggested to the evaluation patients; the supplement was not prescribed but presented as an option, possibly capable of improving the management of CVI.
2. The supplement was only used on top of what was considered at the time of the "standard" or "best-management/care," if available, for that condition, according to relevant international guidelines.
3. The use of the supplement should not interfere with any other treatment or preventive measure.
4. The period of follow-up is considered variable, according to the needs and availability of the patients or registry patients. The observation period could be therefore variable, not prefixed. Supplement administration should be used as long as needed to see results or changes.
5. The type of evaluation for these studies is always a registry; there is no intervention from the observers.
6. The supplement is available without prescription and may be voluntarily acquired by the study patients.
7. In supplement studies there is no defined group allocation, no randomization organized by the monitors.
8. Patients decide—on the basis of the initial briefing—the management group they want to join including the control (nonsupplement) group. No placebo is used.

Open label. Patients are always informed about the supplement or any treatment and management measure. A possible placebo effect is also carefully explained and considered. Data and results are analyzed only after the observation period—ideally, when sufficient evidence is collected or when fund limitations would eventually stop the collection of the observations.

Characteristics of the registry. This study was independent; the evaluation products were not prescribed but recommended. A supplement registry is actually more corresponding to real, practical conditions than most clinical studies that select groups of patients in selected conditions, often not corresponding to an epidemiologic reality.

This type of supplement studies may be particularly suited for emerging countries and when expensive sponsorships for brand products are not available.[28–30]

External study reviewers. All results and data were evaluated by an external reviewing panel, not in contact with the registry patients.

Supplementation/management with the registry products effectively controls signs and symptoms associated with CVI. The definitive treatment is the surgical (including sclerotherapy) corrections of the most incompetent segments. This type of patients should be treated with interventional methods, but some patients do not want surgery for a conditions that it not life-threatening. Many prefer to delay interventions and most hospital have long waiting list for venous surgery that is not considered urgent. Often, for most patients the only option is private surgery that is not financially possible for all patients. Therefore, there are long delays and periods before (and also after surgery) that may have benefits from supplementary medical management.

In CVI, edema may be persistent and associated with significant signs that may alter the life of most patients and, in time, cause distal complication and even ulcerations if not properly managed. Elastic stockings are effective, but in a warmer day (>25°C, i.e., ~5 mo/y in Southern Europe) it is difficult to work or operate all the time with compressive stockings. Their compliance is therefore relatively low. Management of CVI should include other obvious steps, including weight control, diet, sodium restriction, exercise, and avoiding prolonged standing or sitting positions.[4,32] Self-medication particularly with nonprescription products and with PS supplements is becoming an important step.[31–33] All these venoactive products are very safe, and most patients may directly start supplementation evaluating after a period of weeks whether there is a positive effect on their specific conditions. Not all PS supplements and management act in the same way in different patients.[30] The principle of individualized medicine (one of the main target aims of this type of registry) is the direct evaluation by patients of the effects of the supplementation on their condition.[31,33] Different products may produce different individual results.

Pycnogenol (the standardized extract of French Maritime Pine Bark) has been tested and used in several types of patients with CVI, symptomatic varicose veins, and in postthrombotic syndrome.[34] It has shown significant efficacy particularly on the microcirculation and on distal leg edema (the hallmark of CVI) in several studies.[17,21] Venous edema is very positively affected by Pycnogenol supplementation. The effects are comparatively larger with Pycnogenol in comparison with what is observed with other venoactive compounds.[34] Recent studies have also indicated a limited but significant antithrombotic activity of Pycnogenol that may even protect patients with CVI and varicose veins from thrombotic complications. An antiplatelet activity has been documented in previous studies. Venoruton and *Antistax (GLE)*[35] have been used for symptoms related to varicose veins and CVI and are popular, safe self-treatments in several countries. The potency of Pycnogenol is much higher (almost 10 times) than most other products as almost similar (microcirculatory and clinical) effects can be obtained with 100 mg of Pycnogenol or doses of 1 g with other products.

The *costs of supplementation* should be better evaluated in longer studies as these products, generally, are not reimbursed by health care providers but directly paid by the patients. All the studied product can now be easily obtained on qualified Web sites. Comparative evaluation of dose-related positive effects (targeting microcirculatory, objective parameters) are in progress as well as the evaluation of the efficacy of these products in longer studies.

It is interesting to observe that this registry study was organized and completed without any interaction with the producers of the products that do not seem interested in a comparative or cost analysis.

The evaluation of oxidative stress (in the peripheral blood, at the perimalleolar region) may also explain, in time, some of the effects of desaturated, pooling blood in the distal venous system and the evolution of skin complications.

The absorption of these products may also require a defined pharmaceutical preparation and a *metabolic platform* (i.e., including mineral, elements, and formulations able to offer better and consistent absorption and distribution). Most of these products are not easily absorbed and often destroyed in large quantities in their intestinal passage; their metabolism (being multiple molecular cocktails) could be erratic.

Noninterference studies. A larger study is including noninterference evaluations. These products are used for long periods of time and some patients may use other common products (i.e., anticoagulants, antiplatelet agents, antihypertensive agents, cholesterol lowering products).

A noninterference study indicates that Pycnogenol does not alter either treatment with antiplatelet agents or anticoagulants.[34] A study on edema shows that Pycnogenol controls edema induced by angiotensin-converting enzyme (ACE) inhibitors. Also, comparable studies are in progress with Venoruton and show comparable patterns. A new noninterference study shows that Antistax treatment is compatible both with antiplatelet agents and anticoagulants and it does not change the usual dosages.[35]

The CEAP classification is minimally affected in these studies and—excluding some symptoms—usually does not significantly change with pharmacologic management or compression.

In conclusion, medical managements with several venoactive and antiedema products is effective, safe, and useful, and constitute complementary managements for venous patients to be used in synchrony with interventional treatments and compression and lifestyle changes to improve the quality of life of most patients.

All products have a significant efficacy. Pycnogenol appears to be the most potent product and definitely in most contexts (i.e., microcirculation and edema control) the most effective. Pycnogenol and the combination VE-PY are competitively better in comparison with all other products and with stockings showing a good performance in most tests. The efficacy of Pycnogenol and the combination are competitive with elastic compression that does not have the same level of tolerability, especially in warmer climates. A larger and more prolonged evaluation is in progress to evaluate cost efficacy (and noninterference with drugs) of these types of products in the management of CVI using as target the occurrence of the most possible severe complications.

Conflict of Interest

There is no conflict of interest for any of the authors. The study was completely managed by the University or Institutional Grants. There was no interference by the producers.

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