A Clinical Comparison of Pycnogenol, Antistax, and Stocking in Chronic Venous Insufficiency

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Abstract

This 8-week registry study was a comparative evaluation of Pycnogenol (French Maritime Pine Bark extract; Horphag Research, Geneva) and Antistax (grape leaf extract [GLE, Boehringer Ingelheim, Germany]) in controlling symptoms of chronic venous insufficiency (CVI). “Standard management” for CVI is compression; a group of comparable subjects was monitored to evaluate the effects of stockings. The registry included 183 patients (166 completing). Supplementation with Antistax (two tablets of 360 mg/d) or Pycnogenol (100 mg/d) was used. The groups were comparable for age, symptoms, venous incompetence, and microcirculation (with increased capillary filtration and skin flux) at inclusion. At 8 weeks, the rate of swelling ($p < 0.05$) and skin flux decreased toward normal values; changes were more important with Pycnogenol ($p < 0.05$). Transcutaneous P_{O_2} was increased more with Pycnogenol ($p < 0.05$). Ankle circumference was decreased more ($p < 0.05$) with Pycnogenol. An analog scale quantified symptoms. At 8 weeks, pain and edema were decreased with Pycnogenol and elastic compression ($p < 0.05$) with prevalence for Pycnogenol ($p < 0.05$). Edema with Pycnogenol was decreased by 40%. Induration was reduced only in the Pycnogenol group ($p < 0.05$) with minimal variations in the other groups. Tolerability and compliance were optimal. Elastic compression was correctly used by 80% of the patients indicating that it may be more difficult to use, particularly in warmer days. Costs for Pycnogenol were lower (96; 3.3 Euros) in comparison with the other groups (132; 1.4 Euros for GLE and 149; 2.2 Euros for compression).

Keywords

- edema
- venous insufficiency
- supplements
- Pycnogenol
- Antistax
- Stockings

Venous disease and chronic venous insufficiency (CVI) are very common clinical conditions associated with impaired venous return causing discomfort, edema, and skin changes.^{1,2} Causes of CVI are deep venous thrombosis (DVT) and conditions resulting in venous hypertension (large untreated varicose veins), alterations in competence, venous valve disruption (i.e., after DVT).^{1,2} Diagnosis of CVI is mainly clinical and is defined by ultrasound.^{1–3} CVI is socially very relevant as it affects some 5% of patients in the United States of America. According to the Merck Manual,³ the standard management (SM) of CVI is based on elastic compression, leg elevation, when possible, topical treatments and skin management and interventions (surgery or sclerotherapy). Drugs to treat CVI are available and may

be used to improve signs and symptoms. Several compounds—of natural origin, considered supplements—are available to manage CVI in the different stages, to control signs and symptoms. Compression cannot be used in all patients all the time and it is difficult to bear in summer or in hot climates.

Pycnogenol,⁴ a branded French Maritime Pine Bark extract (a registered trademark of Horphag Research, Geneva), has been used as a supplement in patients with symptomatic varicose veins and in CVI. It has shown a significant effect even at low dosages (100 mg/d). The effects of Pycnogenol on edema have been documented in several studies. Edema and other signs of CVI are comparatively more improved by Pycnogenol than by other compounds.⁴

Products based on vine leaves, have been also used to control symptoms of CVI.^{5–9} A recent study using a dose⁵ of 720 mg/d of Antistax (a registered trademark of Boehringer-Ingelheim, Germany) for 12 weeks has evaluated patients with CVI (CEAP grades 3–4a)¹⁰ and moderate–severe clinical symptoms. Efficacy end points were changes in limb volume (detected by water displacement volumetry), CVI symptoms assessed on an analog scale and global efficacy evaluations.

The aim of this supplement registry study was a comparative, parallel evaluation of Pycnogenol and Antistax (GLE) in controlling signs and symptoms of CVI in an 8-week study. “Standard management” for CVI is generally compression;^{1,3} therefore, another group of comparable subjects with CVI was monitored to evaluate the comparative effects—and tolerability—of elastic stockings on CVI in the same period of time.

The registry included 183 comparable patients (166 completing 8 weeks) with CVI and symptoms (CEAP grades 3–4a; moderate–severe symptoms as in ►Table 1). Antistax was used at the recommended dosage (two tablets of 360 mg/d) and Pycnogenol was used at the dosage of 100 mg/d.

Subjects and Methods

The registry was based on objective technical measurements useful to quantify CVI (CEAP grades 3–4a) with moderate–severe clinical symptoms and on the monitoring of clinical attributes specific of CVI. Of the 200 preselected comparable subjects (otherwise healthy, not using any drug) 183 were included (17 were excluded for logistical or personal problems); 166 completed the 8 weeks (61 in the Pycnogenol group, 55 in the GLE group, and 50 using elastic compression) (►Table 2).

Ambulatory venous pressure (AVP) including the RT (refilling time in seconds). These two measurements express the lowest pressure obtained during a 10 tiptoe standing test and the following time needed to refill the venous system at the end of the exercise test. The microcirculation was evaluated (at standard temperature of 22°C) at the internal perimaleolar

region using a laser Doppler flowmeter (Laserflo, Vasamedics, St. Paul, MN). The resting flux (in flux units) was measured (as a continuous measurement over 1 minute of recording, after 3 minutes of stabilization). The rate of ankle swelling (in mL/min/100 ml of tissue) was measured with a strain gauge plethysmograph (Hokanson SPG 16, Hokanson, Bellevue, WA). The patient was resting supine for 10 minutes and then asked to stand. A strain gauge had been applied at the lower ankle circumference at the nonsupporting limb, with patient holding onto a frame. Transcutaneous PO₂ was measured at the internal perimaleolar region with a Kontron CombiSensor (Kontron, Cambridge) after 20 minutes of heating of the probe at 40°C. Ankle circumference was measured by patients (in cm) with a tape, in the morning at 8 AM, at the minimal ankle circumference. All standards and reproducibility values for these measurements have been established in several previous studies and described in details in the previous publications.^{10–15}

The clinical attributes linked to CVI are shown in ►Table 1. The attributes were rated by the physician on a visual analog scale line from 0 (none/absent) to 3 (severe). CVI had been present—with increasing levels of gravity—in all the subjects for more than 10 years. The variations in Venous Clinical Severity Score included 10 items. By inclusion criteria, subjects did not have any clinically significant pigmentation of inflammation and had no history of ulcers. They, however, all had need for compression considering the presence of edema in all the affected limbs. Only subjects with both limbs affected by CVI were included. Obese patients were excluded (the body mass index had to be at inclusion < 25 kg/m²).

No previous DVT or postthrombotic syndrome had been recorded or documented at inclusion. Duplex ultrasound at inclusion had indicated that the deep venous system was intact and that there was no significant obstruction (as also seen with AVP measurements) with a predominant venous incompetence at superficial level.^{16–18} Previous limited surgery (excluding stripping) and/or sclerotherapy had been made at least 1 year before the start of the registry. All

Table 1 Clinical attributes based on VCSS^a

Ratings	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
1 Pain	None	Occasional	Daily	Limiting activities	
2 Varicose veins	None	Few	Scattered	Multiple (LSV)	
3 Venous edema	None	Evening, ankle	Afternoon, lower leg	Morning, all leg	
4 Pigmentation	None	Limited area	Wide (lower 1/3)	Wider (above 1/3)	Not included
5 Inflammation	None	Cellulitis	Cellulitis	Cellulitis	Not included
6 Induration	None	Focal (< 5 cm)	< lower 1/3	Entire lower 1/3	
7 Number of ulcers	None	1	2	3	Not included
8 Duration of ulcers	None	< 3 mo	3 mo–1 y	> 1 y	Not included
9 Size of ulcers	None	< 2 cm diameter	2–6 cm diameter	> 6 cm diameter	Not included
10 Need for compression	None	Intermittent use	Most days	Continually	

Abbreviations: LSV: long saphenous vein; VCSS, Venous Clinical Severity Score.

^aRegistry subjects ranged between mild and severe.

Table 2 Of 200 preselected comparable subjects with CVI and no other clinical conditions, 183 were included in the study and 166 completed the 8 wk

		Inclusion	8 wk	Lost	p
Number	Pycnogenol	63	61 (females 34)	2	ns
	Antistax	62	55 (females 31)	7	ns
	El compression	58	50 (females 12)	8	
Age (Mean and SD)	Pycnogenol	43.3;5.5			ns
	Antistax	42.6;6.4			ns
	El compression	42.5;3.2			
AVP (mean and SD with range)	Pycnogenol	58;7.3 mm Hg (range, 48–60 mm Hg)			ns
	Antistax	57.8;6.7 (47–61)			ns
	El compression	57.9;5.6 (46–60)			
RT (s) (mean and SD)	Pycnogenol	< 12 s (average 7.2;2.2 s)	7.1;1.1		ns
	Antistax	< 12 s (7.3;2)	7.2;1.2		ns
	El compression	< 12 s (7.4;2.2)	7.3;1.6		
Duration of disease (mean and SD)	Pycnogenol	16.0;3.1 y			ns
	Antistax	15.87;3.4			ns
	El compression	15.8;2.2			
Days of follow-up: in the registry (mean and SD)	Pycnogenol	62.3;2.3			ns
	Antistax	61.5;1.3			ns
	El compression	62.2;2			

Abbreviations: AVP, ambulatory venous pressure; CVI, chronic venous insufficiency; El, elastic; GLE, grape leaf extract; RT, refilling time; SD, standard deviation.

Note: ns, indicates that the values are not different from the Elastic compression (control) group.

subjects were on a waiting list for surgical treatment and/or sclerotherapy.

Antistax (tablets 360 mg) contain as active ingredient red grape leaf extract (GLE). According to the producer, GLE taken every day helps reducing the feelings of aching, heavy and tired legs associated with working lifestyles and prolonged daily standing or sitting in the same position for long periods. Claims include maintaining a healthy circulation in leg veins. The active elements in Antistax (GLE) are derived from a specific red vine leaf extract. The extract should help ensure that the walls of the veins in the leg have a physiological function. This product also should act by keeping the extracapillary fluid within normal values even after prolonged standing or sitting. This effect on edema helps maintaining a normal venous flow and controls symptoms (tired, heavy, and aching legs). The GLE includes red vine leaf compounds (195 mg). Antistax, in the clinical studies,^{5–9} has shown that beneficial, therapeutic effects can be observed after 3 weeks. The maximum therapeutic effect is expected after 4 to 6 weeks of continuous use. The recommended dosage of Antistax is two capsules/d for at least 6 weeks.

Supplement studies^{19–23} define activities of supplements. The fields of application for supplements are mainly preclinical, borderline applications, and supplementary management of some clinical or preclinical conditions. These studies

compare data based on the “standard management” (SM) or to other management plans. In this registry, supplementation was suggested, not prescribed but presented as an option, possibly capable of improving the management. The supplement was used on top of the SM. Supplement are available in the market without prescription and could be voluntarily acquired by the study subjects; there is no group allocation, no randomization organized by the monitors. Subjects decide—on the basis of the initial briefing—the management group they want to join. No placebo is used. This study is a small-scale, pilot, registry study. All results were evaluated by an external reviewing panel, not in contact with the patients. Sponsorship from the producers of the tested products was not available.

Safety and tolerability were assessed by weekly phone and mail contacts and laboratory measurements. Adverse experiences (requiring medical intervention) were evaluated throughout the registry and communicated to the monitor as soon as possible by message through phone.

Compression

In the “standard” management group, below-knee stockings (Sigvaris, Wintertur, Switzerland; compression at the ankle 25–30 mm Hg) were used daily, during working activities and removed only for bed rest. The use of higher compression in

walking patients, otherwise healthy is less tolerated, particularly in warmer climate; it should be considered when complications (inflammation, pigmentation, lipodermatosclerosis, previous ulcerations or impending ulcerations, previous thrombotic episodes, and reduced mobility) are present or impending. Lighter compression is better tolerated, stockings are easier to wear and their costs are limited. In case of CVI associated to deep venous incompetence a higher level of compression is also indicated.^{13–15} “Standard management” of CVI—for this type of patients without complications—includes other steps (weight control, an appropriate diet with sodium restriction, regular exercise, avoiding prolonged standing or sitting positions, avoiding trauma in areas affected by venous hypertension, and, generally a healthier and less sedentary life).

A simple diary recorded the use of drugs prescribed by the patient's physician (in case this event happened) according to needs. Treatments, other management costs, or disease-related costs (including work disruptions, consultations, tests, and hospital admissions) occurring during the registry period were also recorded if occurred. This type of monitoring is used to evaluate the clinical individual needs and choices in specific subjects.^{24,25}

Pycnogenol supplementation—in previous venous studies—has been shown to be effective in different degrees of venous and microcirculatory disorders^{4,26–33} with great safety and a specific action of peripheral edema (the hallmark of venous diseases, associated to most symptoms in patients with chronic, and severe venous disease).^{1–3}

Statistical Analysis

All resulting values were considered nonparametric. Results were analyzed in comparison with the results from the SM (compression) considered as a baseline. Intra- and intergroup comparisons were performed by nonparametric tests and the ANOVA test, as appropriate. A *p* value less than 0.05 was considered statistically significant. According to the previous studies on comparable groups, at least 30 subjects were considered adequate to define a difference in target outcomes (considering microcirculatory measurements and the scales values) at 8 weeks.

Results

► **Table 2** shows details and distribution of the subjects in the groups followed up in the registry.

As indicated all 200 preselected subjects were in a waiting list for surgical treatment: 183 were included and 166 completed the 8 weeks. The 17 subjects lost were unable to follow the study for logistical reasons or because they decided to have surgery or sclerotherapy (8 subjects). The groups (► **Table 2**) of completing subjects were comparable for age and sex distribution and for their clinical aspects. ► **Table 3** shows data concerning previous interventions (minor surgery or sclerotherapy) on the varicose veins. The groups were also comparable for the type and distribution of incompetence.

► **Table 4** shows the changes in the impaired microcirculation because of the chronic venous hypertension (increased capillary filtration and increased skin flux) compared to inclusion. At 8 weeks, the RAS decrease was significantly more important in the Pycnogenol group ($p < 0.05$). The decrease in skin flux toward normal values was significantly more important in the Pycnogenol group ($p < 0.05$) and transcutaneous Po_2 was improved (increased) more in the Pycnogenol group ($p < 0.05$) with minimal variations in the other two groups. Ankle circumference (basically, a visual expression of edema) was decreased significantly more ($p < 0.05$) in the Pycnogenol group in comparison with the other two groups. ► **Table 5** shows the analog scale line variations in the main symptoms. At 8 weeks, pain was decreased in Pycnogenol subjects and in the group using elastic compression ($p < 0.05$) with a significant prevalence for Pycnogenol ($p < 0.05$). There was no difference at 8 weeks, as expected, in the pattern and distribution of varicose veins in the three groups. Venous edema was significantly decreased in the Pycnogenol and elastic compression group with prevalence for Pycnogenol (–40% in comparison with the initial values) ($p < 0.05$). Induration was significantly reduced only in the Pycnogenol group ($p < 0.05$) with minimal variations in the other two comparative groups. Also, the need for compression was reduced ($p < 0.05$) with Pycnogenol.

Safety

There were no clinical adverse experiences; no side effects were observed. Tolerability was optimal (no patients had to stop the supplementation, compression, or the management plan). Compliance was also optimal with 97% of Pycnogenol capsules correctly used and 93% of the Antistax tablets correctly used. In the patients' diaries, there was no recorded use of any prescription drugs, locally applied product, or

Table 3 Main observations (number of subjects out of the completing group) at inclusion^a

	Pycnogenol	Antistax	Elastic compression
Previous (local) surgery	24/61	22/55	24/50
Sclerotherapy	26/61	24/55	25/50
Superficial venous incompetence	61/61	55/55	50/50

Abbreviation: GLE, grape leaf extract (Antistax).

Note: The groups were comparable for previous treatments.

Table 4 Microcirculatory observations at inclusion and 8 weeks in the internal perimalleolar region (mean and SD)

		Inclusion	8 wk	p
Microcirculation				
RAS (mL/min/100 mL of tissue) (Straingauge plethysmography)	Pycnogenol	2.113;0.11	1.120;0.06	*
	Antistax	2.102;0.13	2.112;0.12	ns
	El compression	2.112;0.12	2.007;0.1	ns
Resting flux (flux units) (Laser Doppler)	Pycno	3.1;0.9	1.6;0.8	*
	Antistax	3.03;0.9	2.39;1.1	*
	El compression	3.01;0.8	2.3;0.9	*
Transcutaneous Po ₂	Pycno	47.7;2.1	52.4;1.2	*
	Antistax	48;1.2	48.1;2.1	ns
	El compression	47.5;3.2	47.4;1.6	ns
Morning ankle circumference (in cm) (Self-measured)	Pycno	21.7;1.8	19.3;1	*
	Antistax	21.2;2.1	21.1;1.1	ns
	El compression	22.1;2	19.3;1.1	*

Abbreviations: El, elastic; GLE, grape leaf extract; RAS, rate of ankle swelling.

* $p < 0.05$.

other supplement during the registry. No hospital admissions were observed in the registry. Elastic compression was correctly used (at least 8 hours/day) by 80% of the patients using compression. This observation may indicate that compression is intrinsically more difficult to use, particularly when climate or days get warmer.

Estimated costs of the Pycnogenol supplementation at 8 weeks were lower (96;3.3 Euros on average) in comparison with the other two groups (132;1.4 Euros in the Antistax group and 149; 2.2 Euros in the compression group). However, the evaluation of costs, including complications, working impairment, distractions from normal activity, and time/

Table 5 Variations in Venous Clinical Severity Score (VCSS) (mean and SD)^a

Attribute	Moderate = 2	Severe = 3		Inclusion	8 Weeks	p
Pain	Daily	Limits activities	Pycnogenol	2.11;1.1	0.3;0.2	*
			Antistax	2.15;1	2.1;0.9	ns
			EL COMP	2.2;1.1	1.9;0.8	*
Varicose veins	Multiple (LSV)	Extensive (LSV + SSV territories)	Pycnogenol	2.5;0.3	2.4;0.3	ns
			Antistax	2.4;1	2.4;1.1	ns
			EL COMP	2.4;2	2.39;1	ns
Venous edema	Afternoon, leg	Morning all leg	Pycnogenol	2.2;0.9	1.3;0.4	* –40%
			Antistax	2.4;1	2.34;0.4	ns
			EL COMP	2.19;0.9	1.6;0.8	*
Induration	<Lower 1/3	Entire lower 1/3	Pycnogenol	2.3;0.9	1.4;0.4	*
			Antistax	2.2;0.4	2.2;0.5	ns
			EL COMP	2.15;0.3	2.1;0.2	ns
Need for compression	Most days	Continually	Pycnogenol	2.2;0.3	1.6;0.2	*
			Antistax	2.11;0.5	2.02;0.3	ns
			EL COMP	–	–	

Abbreviations: EL COMP, elastic compression; GLE, grape leaf extract; Lower 1/3: lower one-third of the leg; LSV: long saphenous vein; SSV: short saphenous vein.

^aBy inclusion criteria, subjects did not have any clinically significant pigmentation of inflammation and had no history of ulcers. They, however, had edema indicating the need for compression or supplementation.

*Mann–Whitney U-test = $p < 0.05$ (comparison between two groups).

money wasted for extra tests, consultations, and treatments require a larger group and a longer period of evaluation.

Discussion

The combination of macro- and microcirculatory parameters with a scale evaluation of the major symptoms is an important model to evaluate CVI and the effects of treatments on CVI. Results indicate that improvements in microcirculation and the reduction in edema are the main factors in controlling and improving symptoms. The number of varicose veins and AVP measurements would not change in 8 weeks with conservative treatments but the perception of symptoms, particularly those caused by swelling, may be significantly affected in symptomatic subjects. The actual, definitive treatment for these patients is the control of reflux either with surgery or sclerotherapy and, if not possible or indicated, with elastic compression. It is important to observe that it is not easy to find a group of 200 subjects not using other treatments and without any other clinical condition and able and interested in a registry. The use of a single management method (i.e., supplementation of compression) may be correctly evaluated only in subjects not using other products (i.e., antihypertensive agents may affect the microcirculation, edema measurements, and swelling).

This registry indicates that subjects using Pycnogenol supplementation may have a significant benefit on the microcirculation and on the most common¹⁻³ complaints associated with CVI even in a relatively short period (8 weeks). Supplementation controls symptoms associated with CVI. The definitive treatment is the surgical (including sclerotherapy) corrections of the most incompetent segments, if possible. However, edema may be persistent and associated with significant signs that may alter the life of most patients. Elastic stockings are also effective but on a warmer day (i.e., approximately 5 months/year in Southern Europe) it is difficult to work or operate all the time with compressive stockings. Management of CVI should include other obvious steps including weight control, diet, sodium restriction, exercise, and avoiding prolonged standing or sitting positions.

Self-medication with supplements is an important step. Supplements are safe and most patients may directly start supplementation evaluating after days or a period of 1 to 2 weeks whether there is a positive effect on their specific conditions. Not all supplements and management act in the same way in different patients. The principle of individualized medicine (and the main aim of this type of registry) is the evaluation by the patients themselves of the effects of the supplementation on their condition.

Pycnogenol (the standardized, proprietary extract of French Pine Bark) has been tested and used as a supplement in several types of patients with CVI, symptomatic varicose veins, and in postthrombotic syndrome.⁴ Pycnogenol has shown significant efficacy particularly on the microcirculation and on distal leg edema (the hallmark of CVI) in several studies.²⁶⁻³³ Venous and lymphatic edemas are very positively affected by Pycnogenol supplementation.

The effects are comparatively larger with Pycnogenol in comparison with what is observed with the management with other venoactive compounds.⁴

Pycnogenol is considered ideal for self-medication and for the individualized management of CVI. Recent studies have also indicated a significant antithrombotic activity of Pycnogenol that may even protect subjects with CVI and varicose veins from some thrombotic complications.

Antistax (GLE) has also been used for the management of signs and symptoms associated to varicose veins and CVI and it is a popular treatment or remedy in several countries. The product is safe and well tolerated. However, the potency of Pycnogenol is much higher as 100 mg of Pycnogenol produces better (microcirculatory and clinical) effects as 720 mg of Antistax.

The costs of supplementation should be better evaluated in longer studies as supplements are not reimbursed by health care providers and have to be directly bought by the patients. Comparative evaluation of dose-related positive effects (targeting microcirculatory, objective parameters) is in progress as well as the efficacy of both these products in longer studies.

Conclusion

This registry indicates that supplementation with Pycnogenol appears to be effective and competitively better in comparison with GLE and even with elastic compression.

A more prolonged evaluation is suggested to evaluate cost-efficacy of these types of products in the management of CVI.

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