

A multicenter randomized controlled trial evaluating balneotherapy in patients with advanced chronic venous insufficiency

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Background: Apart from compression therapy, physical therapy has scarcely been evaluated in the treatment of chronic venous disorders (CVDs). Spa treatment is a popular way to administer physical therapy for CVDs in France, but its efficacy has not yet been assessed in a large trial. The objective was to assess the efficacy of spa therapy for patients with advanced CVD (CEAP clinical classes C4-C5).

Methods: This was a single-blind (treatment concealed to the investigators) randomized, multicenter, controlled trial (French spa resorts). Inclusion criteria were primary or post-thrombotic CVD with skin changes but no active ulcer (C4a, C4b, or C5). The treated group had the usual 3-week spa treatment course soon after randomization; the control group had spa treatment after the 1-year comparison period. All patients continued their usual medical care including wearing compression stockings. Treatment consisted of four balneotherapy sessions per day for 6 days a week. Follow-up was performed at 6, 12 and 18 months by independent blinded investigators. The main outcome criterion was the incidence of leg ulcers at 12 months. Secondary criteria were a modified version of the Venous Clinical Severity Score, a visual analog scale for leg symptoms, and the Chronic Venous Insufficiency Questionnaire 2 and EuroQol 5D quality-of-life autoquestionnaires.

Results: Four hundred twenty-five subjects were enrolled: 214 in the treatment group (Spa) and 211 in the control group (Ctr); they were similar at baseline regarding their demographic characteristics, the severity of the CVD, and the outcome variables. At 1 year, the incidence of leg ulcers was not statistically different (Spa: +9.3%; 95% confidence interval [CI], +5.6 - +14.3; Ctr: +6.1%; 95% CI, +3.2 - +10.4), whereas the Venous Clinical Severity Score improved significantly in the treatment group (Spa: -1.2; 95% CI, -1.6 - -0.8; Ctr: -0.6; 95% CI, -1.0 - -0.2; $P = .04$). A significant difference favoring spa treatment was found regarding symptoms after 1 year (Spa: -0.03; 95% CI, -0.57 - +0.51; Ctr: +0.87; 95% CI, +0.46 - +1.26; $P = .009$). EuroQol 5D improved in the treatment group (Spa: +0.01; 95% CI, -0.02 - +0.04) while it worsened (Ctr: -0.07; 95% CI, -0.10 - -0.04) in the control group ($P < .001$). A similar pattern was found for the Chronic Venous Insufficiency Questionnaire 2 scale (Spa: -2.0; 95% CI, -4.4 - +0.4; Ctr: +2.4; 95% CI, +0.2 - +4.7; $P = .008$). The control patients showed similar improvements in clinical severity, symptoms, and quality of life after their own spa treatment (day 547).

Conclusions: In this study, the incidence of leg ulcers was not reduced after a 3-week spa therapy course. Nevertheless, our study demonstrates that spa therapy provides a significant and substantial improvement in clinical status, symptoms, and quality of life of patients with advanced venous insufficiency for at least 1 year. (*J Vasc Surg* 2014;59:447-54.)

In spite of the extensive development of efficient procedures able to improve venous dysfunction in the lower limbs,¹ advanced chronic venous insufficiency (ie,

with CEAP C4-C6 chronic venous disorders [CVDs])² remains a burden for both national health care systems^{3,4} and for patients.⁵ The documented impact of venoactive drugs is limited to an improvement of symptoms.⁶ Most patients have to wear compression stockings, but poor compliance to this treatment shows in itself that it is not the perfect answer to their expectations.⁷ In this context, any adjunctive treatment able to improve the function and quality of life of the patients is welcome.

Although scarcely evaluated for this condition, rehabilitation and physical therapy aimed at a restoration of calf muscle pump function offer potentially useful adjunctive treatments,⁸ and several randomized studies have shown promising hemodynamic results.⁹⁻¹²

Spa treatment is a popular way to administer physical therapy for CVDs in Europe.¹³⁻¹⁵ In France, where more than 40,000 patients are treated annually, it is delivered as a 3-week course of intensive balneotherapy in a spa resort specialized in the treatment of CVD patients; most often associated with a patient education program¹⁶ and is partly reimbursed by French national health insurance.¹⁵

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In a recent monocentric randomized controlled trial,¹⁷ we observed that such spa treatment, performed in the spa resort of La Léchère, was able to improve significantly skin trophic changes in patients with advanced chronic venous insufficiency (CEAP C4-C5), as well as their CVD-related quality of life and symptoms, for at least 1 year. A trend toward a reduction in the incidence of leg ulcers was also observed, but the numbers were too small to reach statistical significance. The aim of the present study was to confirm the efficacy of spa treatment on the physical status, symptoms, and quality of life in patients with advanced chronic venous insufficiency (CEAP C4-C5), in a large-scale multicenter trial, involving the 12 French spa resorts specializing in the treatment of CVD, and in particular, to evaluate its impact on the incidence of venous ulcers.

METHODS

Study design and organization. This was a single-blind (treatment concealed to the investigators) randomized controlled trial with two parallel groups. Patients attended a spa treatment course in addition to continuing their usual medical care. The tested hypotheses were that patients with advanced chronic venous insufficiency (CVD with CEAP C classes C4-C5) would have a decreased 1-year incidence of leg ulcers (primary outcome criterion) and a long-standing improvement (remaining significant at month 12) in their signs, symptoms, and quality of life (secondary outcome criteria) compared with a control group with no spa treatment.

Subjects. Inclusion criteria were primary or post-thrombotic CVD with skin changes but no active ulcer (C4a, C4b, or C5) and evidence of venous incompetence demonstrated by duplex ultrasound examination with at least one significant reflux (of more than 1-second duration in a standing position) in the superficial, deep and/or perforator veins. Patients had to be at least 18 years old and willing to participate (written informed consent) in the study (ie, to attend a 3-week course of spa treatment in one of the 12 French spa resorts treating patients with CVD) (ie, Argeles-Gazost, Barbotan-les-Thermes, Bagnoles de l'Orne, Dax, Evaux-les-Bains, Jonzac, La Léchère-les-Bains, Luxeuil, Luz-Saint-Sauveur, Rochefort-sur-Mer, Saint Paul-les-Dax, and Saubusse) and to accept a follow-up of 18 months' duration including a monthly self-administered questionnaire and a medical examination every 6 months.

Patients were not included if a surgical or endovascular treatment of the venous disease was planned at any time during the entire study period (18 months) or had been performed less than 6 months prior to the inclusion visit. Patients with spa treatment in the previous 6 months or a contraindication to spa treatment (life-threatening disease, cardiac or renal failure, immunodeficiency, psychiatric disorders, severe difficulty walking) were also not included, as well as those with edema of nonvenous origin (clinical lymphedema, cardiac failure, hypoalbuminemia), symptomatic neurologic diseases of the lower limbs

(neurogenic pain or abnormal neurologic examination of the lower limbs) or significant peripheral arterial disease (ankle brachial index <0.70).

Randomization. Centralized randomization was performed immediately after the inclusion visit, and its result was kept hidden from the investigator, with a stratification by center and CEAP C class (C4 vs C5) to ensure better comparability. The treatment took place in the spa resort closest to the patient's home.

Intervention. Patients in the treatment group attended a 3-week spa treatment course in the spa resort closest to their home, soon after randomization. The control group also attended a spa treatment course, but after the comparison period (ie, starting soon after day 365; Fig 1).

The spa treatment course was performed according to the rules of the French health authority, and study patients were cared for in the same way as any other CVD patient, with their participation in the study concealed from resort staff. The treatment regimen consisted of four balneotherapy sessions per day, 6 days a week during 3 weeks, and educational activities that were differently organized in each resort. The balneotherapy sessions included¹⁵ a 15-minute walking session in a specially designed pool with tracks in semideep (80 cm) cool (28°C) water (training of muscle pump function under water compression); a 20-minute whirlpool bath session with automatic air and water massage cycles (aimed at relaxation and mobilization of the superficial skin volume flow); a 10-minute bath session with customized underwater strong massaging jets (mobilization and softening of the sclerotic subcutaneous tissues); and a 10-minute massage session of the leg and ankle skin areas by a registered physiotherapist under a light spray shower (softening of the sclerotic subcutaneous tissues) or a 15-minute joint mobilization session in a deep (150 cm) warm (34°C) pool under the supervision of a physiotherapist (improvement of ankle, and also knee and hip joint mobility for better ambulation and muscle-pump functioning).

Sessions were customized for each patient by the specialist spa physician according to the patient's needs and capabilities on arrival at the spa resort and at the two medical visits systematically performed during the spa treatment course as required by French health authority rules.

Concomitant treatments. During the entire study period, patients in both groups remained in the care of their regular physician, who provided them with any treatment they considered necessary, including wearing compression stockings. No standardized basal treatment or counseling was provided by the investigators.

Main outcome measurements. The follow-up examinations were performed by the same investigator for a given patient every 6 months during the study period, with a final visit at month 18. Before each visit, the patient was reminded by the research assistant that he had to conceal his status regarding the spa treatment from the investigator, to maintain blinding for the evaluation.

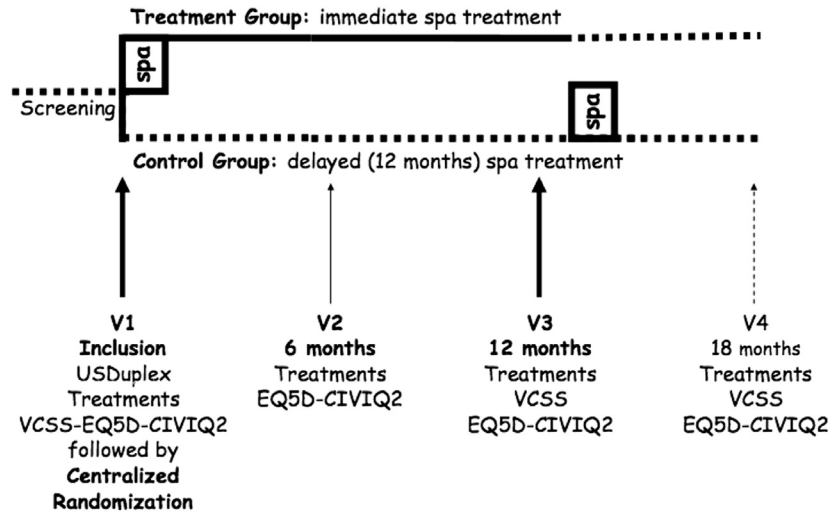


Fig 1. Pseudo cross-over design of the study. The comparison concerns the first year (ie, 1 year after treatment for the treatment group, vs 1 year after randomization but before spa treatment for the control group). *CIVIQ2*, Chronic Venous Insufficiency Questionnaire 2; *EQ5D*, EuroQol 5D; *VCSS*, Venous Clinical Severity Score.

The primary outcome criterion was the 1-year incidence of leg ulcer, defined as a wound to the lower leg involving the dermis, which did not heal within 6 weeks if it was the first in a given skin area, or within 2 weeks for a relapse at the site of a previous ulcer. Photos of the wounds were systematically collected by the investigators, and a critical event committee, consisting of two experienced vascular physicians blinded to any treatment information, validated the diagnosis.

Secondary outcomes. The severity of the venous disease was evaluated using the Venous Clinical Severity Score (VCSS), described by Rutherford et al¹⁸ modified as follows. Spa treatment is a composite treatment that includes patient education, with compliance to compression therapy as one of its aims; the latter was not taken into account in the score calculation but only the parameters related to clinical status, resulting in a modified VCSS ranging from 0 to 27. The score was calculated for both legs and the highest recorded.

Self-evaluation of the intensity of leg symptoms was performed each month by the patient and reported in a diary using two 10-cm visual analog scale (VAS). The intensity of symptoms was rated separately for each leg, from “no discomfort” at the bottom (0.0), to “unbearable” at the top (10.0), according to a method previously described and discussed in detail.¹⁹ The first measurement, taken as baseline, was at month 1; for the analysis, only the VAS of the most severely affected leg was taken into account.

Quality of life was measured every 6 months by the validated French versions of the generic EuroQol 5D instrument²⁰ and the vein-specific self-administered Chronic Venous Insufficiency Questionnaire 2 (CIVIQ2), a disease-specific quality-of-life instrument dedicated to CVDs and validated in French for this condition.²¹ In

addition to the overall CIVIQ2 scale, its four components (pain, physical, psychological, and social components) were separately analyzed.

Data regarding the direct cost of medical and nursing care were recorded for subsequent medicoeconomic analysis, but are not reported in this article.

At each visit, any adverse events were recorded and any change in the patient’s treatment. The diagnosis of erysipelas²² and venous thromboembolic events were blindly evaluated by the critical event committee in the same way as for the leg ulcers.

All data (including images) were recorded using an electronic case report form with automated controls (Clininfo) to minimize data capture errors and to allow immediate quality control.

Data management and statistical analysis. Study coordination, monitoring visits to each center, data management, data entry from patient questionnaires, and data analysis were performed by the Grenoble Clinical Research Center. Data managers were blinded to the randomization, including for the final data review regarding protocol deviations and missing data.

The main outcome analysis was conducted as intention to treat. The primary and secondary outcome criteria were assessed at 12 months. The final examination at month 18 was analyzed as a supplementary evaluation of the early effects of spa treatment in the control group.

The statistical analyses were performed with Stata (v. 12; StataCorp, College Station, Tex). Qualitative variables are presented as the number and percentages and continuous variables by the mean and 95% confidence interval. A χ^2 test was performed for categorical data such as the incidence of leg ulcers and Fisher exact test if necessary. For quantitative variables, Student *t*-tests were performed on the differences M12-M0 (and M6-M0).

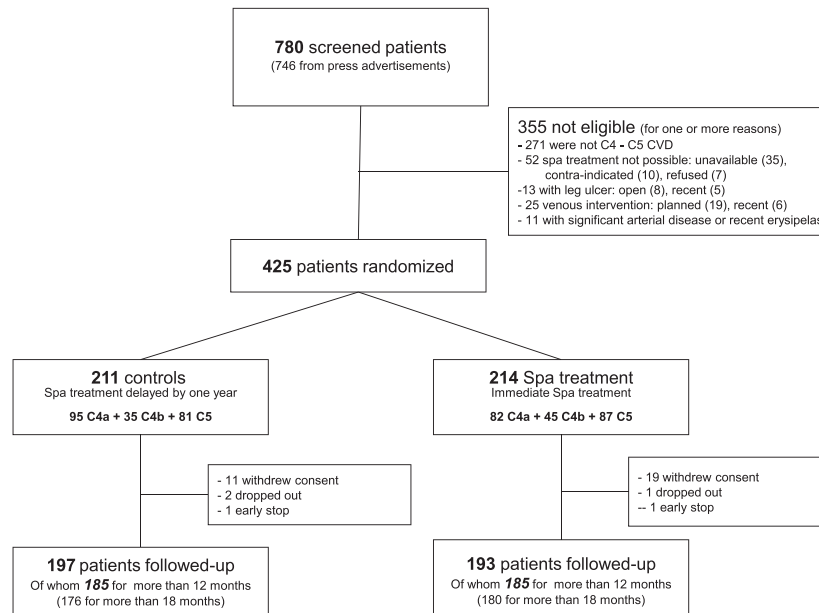


Fig 2. Study flow chart. CVDs, Chronic venous disorders.

The number of subjects to be included was calculated from the expected reduction in the incidence of leg ulcers, which required more patients than the other end points. Our hypothesis was based on a yearly incidence of 20% in the control group compared with 10% in the treated group, with an alpha risk of 5% and a power of 80%. One hundred ninety-nine subjects were needed for the comparison, and we decided to include 440 patients to allow for dropouts.

The study protocol was approved by the regional ethics committee institutional review board 11263 (Comité de Protection des Personnes Sud-Est II) on April 11, 2008 and the French regulatory authorities (ANSM) Eudract N° 2008-A00197-48. It was registered on <http://www.clinicaltrials.gov>: NCT00838500.

RESULTS

Description of the subjects and interventions. The study flow chart is shown in Fig 2. Out of the 780 patients screened for inclusion, most (746) were in response to advertisements in the regional press, and 355 of these were found to be ineligible mainly because they did not show C4 or C5 CVD ($n = 271$); were not available for a spa treatment ($n = 35$); refused ($n = 7$); had a contraindication to spa treatment ($n = 10$); had an open ($n = 8$) or a recent leg ulcer ($n = 5$); had peripheral arterial disease, peripheral neuropathy, or recent erysipelas ($n = 11$); or had a recent ($n = 6$) or planned ($n = 19$) venous intervention or had recent spa treatment ($n = 2$).

The comparison of randomized subjects is shown in Table I. Similar distributions of demographic and prognostic as well as baseline criteria were found in both groups.

Nine patients in the “spa treatment” group did not attend their spa course; nevertheless, they are included in the analysis (intention-to-treat approach). The delay between randomization and spa therapy ranged from 3 to 74 days (median, 24 days). The most frequently attended spa therapy sessions were the whirlpool bath (88%), the in-water walking sessions (81%), the underwater massage (79%), and the light shower massage (28%). Sixty-six percent attended a therapeutic education program. Appendix I (online only) gives further details of the spa treatments.

Forty-six patients from the control group did not attend the spa treatment course, whereas 29 subjects from the treated group attended a second spa course at their own initiative (nine before the end of the first year), because they thought they had benefited from this treatment and did not want to wait for 2 years (due to the seasonal activity of the spa resorts) before repeating it. These deviations had little effect on the outcome criteria, since they mostly occurred after the planned 12-month comparison period; however, they could substantially influence the observations during the poststudy follow-up (months, 13-18).

Incidence of leg ulcers. No difference regarding the 1-year incidence of leg ulcers was found between the groups, or between their C4 and C5 subgroups (Table II).

The physical state of veins, as measured by the modified VCSS, was found to be significantly improved after 1 year in the spa treatment group (Spa: -1.2 ; 95% confidence interval [CI], $-1.6 - -0.8$) compared to controls (Ctr: -0.6 ; 95% CI, $-1.0 - -0.2$; $P = .040$; Fig 3).

Leg symptoms, as assessed by monthly self-evaluation using the VAS, were considerably improved, with a maximal

Table I. Baseline characteristics of patients

Characteristics	Controls (n = 211)	Spa treatment (n = 214)
Male	94 (45)	92 (43)
Age	65.1 (9.2)	63.5 (9.4)
BMI	29.6 (6.1)	30.1 (6.2)
Sequelae of DVT (duplex ultrasound)	105 (50)	100 (47)
Previous spa therapy	45 (21)	37 (17)
Venous incompetence (duplex ultrasound)		
Superficial	173 (82)	181 ^a (85)
Perforator	142 (67)	148 (69)
Deep	103 (49)	97 (45)
CEAP "C" classification		
C4a	95 (45)	82 (38)
C4b	35 (17)	45 (21)
C5	81 (38)	87 (41)
Treatment (at the time of inclusion)		
Anticoagulant therapy	25 (12)	28 (13)
Venoactive drug	69 (33)	72 (34)
Compression therapy	157 (74)	165 (77)
Level of compression: strength 1-2	136 (89)	135 (85)
Strength 3	15 (9.8)	23 (15)
Strength 4 (strongest)	2 (1.3)	1 (0.6)
Physiotherapy	8 (4)	8 (4)
Outcome criteria		
Modified VCSS	8.2 (3.0)	8.6 (3.1) ^a
EQ5D	0.75 (0.22) ^b	0.72 (0.21) ^b
CIVIQ2	36.5 (19.9)	38.4 (20.2) ^a
VAS ^c	4.83 (2.79)	4.62 (3.05)

BMI, Body mass index; CIVIQ2, Chronic Venous Insufficiency Questionnaire 2; DVT, deep vein thrombosis; EQ5D, EuroQol 5D; SD, standard deviation; VAS, visual analog scale.

Continuous data are presented as mean ± standard deviation and categorical data as number (%).

^aOne missing value.

^bFive missing values.

^cVAS at month M1, n = 151 controls and 143 spa.

Table II. Incidence of leg ulcers at 1 year in both groups, and in the C4 and C5 subgroups

Incidence of leg ulcers at 1 year	Controls, No. (%) [95% CI]	Spa treatment, No. (%) [95% CI]	P
Total population	(n = 197)	(n = 193)	.231
Ulcers	12 (6.1) [3.2-10.4]	18 (9.3) [5.6-14.3]	
C4 subgroup	(n = 120)	(n = 115)	1.0
Ulcers	3 (2.5) [0.5-7.1]	3 (2.6) [0.5-7.4]	
C5 subgroup	(n = 77)	(n = 78)	.194
Ulcers	9 (11.7) [5.5-21.0]	15 (19.2) [11.2-29.7]	

CI, Confidence interval.

effect between months 4 and 6 (Spa: M6-M1 = -0.88; 95% CI, -1.36 - -0.40; Ctr: M6-M1 = +0.14; 95% CI, -0.16 - +0.44; $P < .001$) and remained significantly improved 1 year after treatment (Spa: M12-M1 = -0.03; 95% CI, -0.57 - +0.51; Ctr: M12-M1 = +0.87; 95% CI, +0.46 - +1.26; $P = .009$; Fig 4).

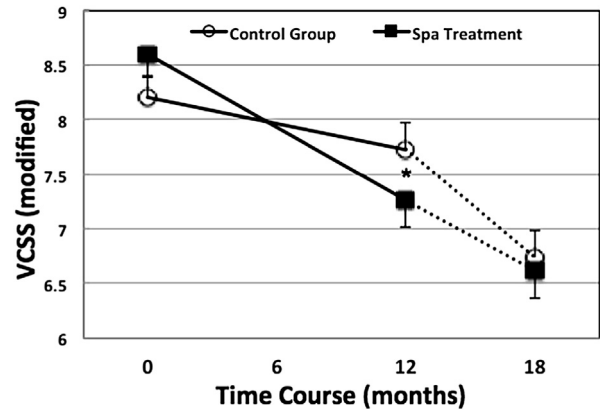


Fig 3. Time course of variations in the Venous Clinical Severity Score (modified VCSS) (mean ± standard error of the mean) (solid lines = comparative period; dotted lines = follow-up) At *: $P < .05$ for the difference with M0. At the end of 1 year, the improvement in VCSS was significantly greater in treated patients than in controls. After 1 year, the control patients were given the spa treatment and their VCSS scores caught up with those of the other group.

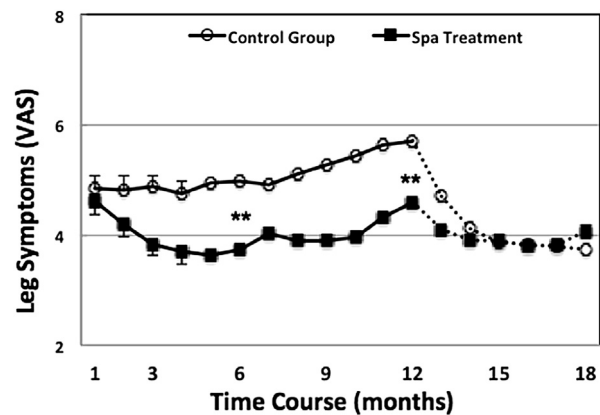


Fig 4. Time course of variations in leg symptoms as assessed by monthly visual analog scale (VAS) (mean ± standard error of the mean) (solid lines = comparative period; dotted lines = follow-up). At **: $P < .01$ for the difference with M0. After spa therapy, the treated group soon experienced a reduction in leg symptoms, which reached a maximum at 4 to 6 months. The difference with the control group remained substantial and highly significant for the entire year. After month 12 and their own spa treatment, the control patients also showed a dramatic improvement in their symptoms.

Vein-related quality of life, as expressed by the CIVIQ2 scale, for which the score decreases when quality of life improves, also improved significantly at 6 months (Spa: M6-M0 = -4.77; 95% CI, -6.88 - -2.66; Ctr: M6-M0 = -0.09; 95% CI, -2.17 - +1.99; $P = .002$) and remained significantly improved at 12 months (Spa: M12-M0 = -2.0; 95% CI, -4.4 - +0.4; Ctr: M12-M0 = +2.4; 95% CI, +0.2 - +4.7; $P = .008$; Fig 5). All four components of the CIVIQ2 scale showed similar

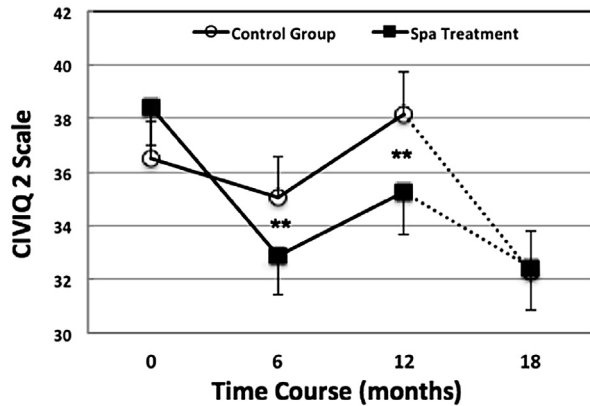


Fig 5. Time course of variations in the venous-related quality-of-life scale Chronic Venous Insufficiency Questionnaire 2 [CIVIQ2] (mean \pm standard error of the mean). Higher scores are related to larger changes in quality of life (solid lines = comparative period; dotted lines = follow-up). At **: $P < .01$ for the difference with M0. In spite of seasonal variations (the spa treatment is performed mostly during summer months), the treated group showed a substantial and significant improvement vs the control group, with the difference remaining significant at month 12. Again, after the control patients were given spa treatment, their CIVIQ2 scale reached the same level as the other group.

patterns but only the physical and the pain subscales showed significant differences at month 12 (Fig 6).

General health-related quality of life, as measured by the EuroQol 5D scale also showed a similar difference at month 6 (Spa: M6-M0 = +0.01; 95% CI, -0.02 - +0.05; Ctr: M6-M0 = -0.05; 95% CI, -0.09 - -0.02; $P = .003$), remaining significant after 1 year (Spa: M12-M0 = +0.01; 95% CI, -0.02 - +0.04; Ctr: M12-M0 = -0.07; 95% CI, -0.10 - -0.04; $P < .001$; Fig 7).

The control group responded in a similar manner to the treatment group to its own postponed spa treatment course (immediately after month 12), with approximately the same magnitude of improvement at month 18 as in the treatment group at month 6, for physical status, symptoms, and quality of life (Figs 3-7).

Compression stockings were used by 76% of patients in both groups as part of their "usual treatment" (see Table I and Appendix II, online only, for details of use during follow-up).

Tolerance. Forty-seven serious adverse events were reported during this 18-month study in the 425 patients, 26 in the control group and 21 in the treatment group. Most (44) were unexpected hospitalizations for various reasons unrelated to the spa treatment according to the investigator. Only five types of severe adverse events (erysipelas, inflammatory lesions, reopening of old ulcer, ulcer recurrence, varicose vein surgery) were possibly or probably ascribed to the spa treatment according to the investigators. One subject in the control group died from esophageal cancer with metastasis.

Particular attention was paid to erysipelas and thromboembolic events in this population. Nine cases of

erysipelas were reported, seven in the treatment group and two in the control group: 5 occurring before or at least 6 months after the spa treatment, 1 occurred during the 3-week spa course, and 3 within 1 month after the end of the spa course. Thirteen patients experienced a thromboembolic event, three in the treatment group and 10 in the control group; most of these events, however, were minor: eight cases of superficial thrombophlebitis, four of distal deep vein thrombosis, and only one clinical pulmonary embolism (in the control group).

DISCUSSION

We found spa treatment to have no effect on the incidence of leg ulcers. Several factors may explain this. (1) The annual incidence of leg ulcers in the control group (6.1%) was more than three times lower than expected (20%, ie, 30% in C5 and 10% in C4 patients) from the literature,²³ and this considerably reduced the power of the study for the primary outcome. (2) The patients enrolled in this study showed good compliance to compression therapy (76%) meeting one of the aims of the American Venous Forum program on the prevention of venous ulcers (75% compliance within 5 years).²⁴ Good compliance could explain both the low incidence of ulcers and the difficulty to demonstrate any additional therapeutic benefit on top of such well-conducted "usual treatment." (3) Spa treatment is a multifaceted health intervention whose educational component may help prevent leg ulcers by improving compliance to usual therapies such as compression therapy. Nevertheless, in this study, spa treatment as currently practiced in France provided no improvement in the incidence of leg ulcers per se at 1 year.

However, for the secondary criteria this large-scale multicenter randomized controlled trial confirms our previous finding in a single-center trial that spa therapy is beneficial as adjunctive treatment to the usual medical care of patients with severe CVD. Our results clearly show a significant improvement in the CVD-related physical status (VCSS), symptoms (VAS), and quality of life (CIVIQ2 and EuroQoL 5D scales). These effects are sustained for at least 1 year.

This trial was not double-blinded. This may be feasible for a comparison of the effects of different mineral waters or for assessing a technical parameter of balneotherapy, but not for evaluating the overall effect of the spa treatment course, which was our aim. Nevertheless, we made all possible efforts to avoid any evaluation bias, with centralized randomization bypassing the investigator, and blinded data management, critical event evaluation and statistical analysis.

The unusual design of the study (Fig 1), with a spa treatment given to the control group following the 1-year comparison period, was adapted from studies of spa therapy for severe low back pain.²⁵ In our previous smaller study,¹⁷ we had found that this approach avoided dropouts in the control group, and we are, thus, able to reasonably rule out a disappointment bias in the control group. The treatment tested was the course of spa therapy taken as a whole, as defined and reimbursed by French health

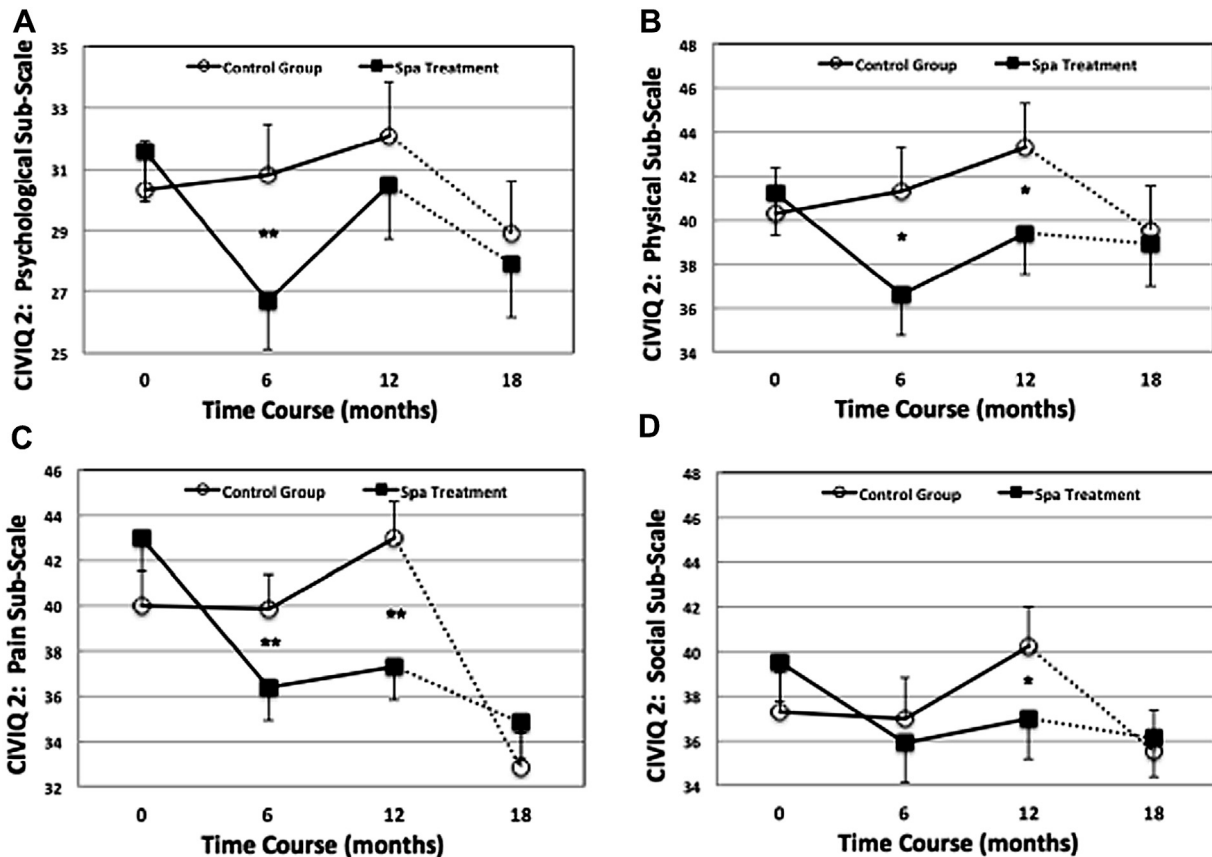


Fig 6. Time course of variations in the four components of the Chronic Venous Insufficiency Questionnaire 2 (CIVIQ2) scale (solid lines = comparative period; dotted lines = follow-up). At *: $P < .05$; and at **: $P < .01$ for the differences with M0. All four subscales of the CIVIQ2 quality-of-life instrument, related to psychological (A), physical (B), pain (C), and social (D) components, were significantly improved in the treated group compared to the controls, with similar time course patterns.

insurance. The results combine the effects of each component of the therapy and their potential synergy but do not allow us to differentiate between the effects of each component, including the possible effects of the nature of the mineral water,²⁶ the therapeutic education,¹⁶ and the psycho-sociological influence of a 3-week health-centered retreat, as well as the intensive active balneotherapy.

In the absence of contraindications,¹⁵ tolerance was very good. Thus, a spa treatment course could be proposed to all patients with advanced chronic venous insufficiencies who are able to invest their time in it, particularly in cases with post-thrombotic syndrome, when the restoration of satisfactory hemodynamic venous function may be difficult to achieve.

CONCLUSIONS

This study confirms our previous smaller monocenter randomized controlled trial. It shows that a spa therapy course, adapted to the treatment of patients with CVD, although not reducing the incidence of leg ulcers, significantly improves their CVD-related physical status, symptoms, and quality of life when used as an adjunct to usual medical care. These effects are large and remain significant

1 year after the spa therapy, justifying its use in patients with advanced chronic venous insufficiency who do not have the possibility of surgical or endovascular treatments.

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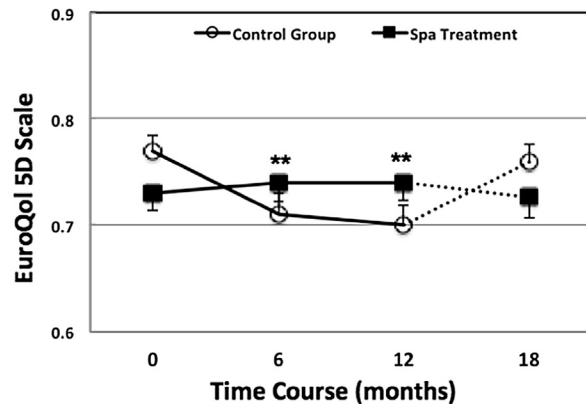


Fig 7. Time course of variations in the generic quality-of-life index EuroQol 5D (solid lines = comparative period; dotted lines = follow-up). At **: $P < .01$ for the difference with M0. The most important variations are seen in the control group, which deteriorates over time, showing a significant difference with the treated group at month 12, but improves after their own spa treatment.

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AUTHOR CONTRIBUTIONS

Conception and design: PC, CG, CR, JB

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Final approval of the article: PC, SB, BS, CG, CR, ChR, JB

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Obtained funding: ChR

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APPENDIX I (online only).

Details of spa therapy

(spa treatment group only)

• In the spa treatment group, 205 patients attended the spa therapy course. The spa treatment physician filled in the spa treatment case report form for 198 patients.

The spa treatment included

Type of treatment	Spa treatment group (n = 198)
Whirlpool bath with automatic air and water massage	175 (88%)
Number of sessions, median [IQR]	18 [18-18] (n = 174)
Controlled walking in semideep water	160 (81%)
Number of sessions, median [IQR]	18 [18-18] (n = 160)
Bath with underwater strong massaging jets	156 (79%)
Number of sessions, median [IQR]	18 [18-18] (n = 156)
Massage by physiotherapist under a light spray shower	56 (28%)
Number of sessions, median [IQR]	9 [9-18] (n = 56)
Simple bath	32 (16%)
Number of sessions, median [IQR]	18 [18-18] (n = 32)
Massage underwater by physiotherapist	11 (6%)
Number of sessions, median [IQR]	18 [9-18] (n = 11)
Application of thermal mud	11 (6%)
Number of sessions, median [IQR]	18 [18-18] (n = 11)
Gymnastics in deep water	10 (5%)
Number of sessions, median [IQR]	9 [8-9] (n = 10)
Other treatments	151 (76%) (n = 198)

IQR, Interquartile range.

APPENDIX II (online only).

Use of compression stockings

Compliance was considered as positive if the frequency of use of compression stockings increased or remained the same when used nearly daily or daily.

Among the 425 patients analyzed, n = 261 patients had compression therapy that had been prescribed by their usual physician at inclusion and at 6 months. Of these, information on their compliance is available at both inclusion and 6 months for n = 238 patients.

Among the 425 patients analyzed, n = 232 patients had compression therapy that had been prescribed by their usual physician at inclusion and at 12 months. Of these, information on their compliance is available at both inclusion and 12 months for n = 217 patients.

Inclusion	Controls	Spa treatment	
Compression therapy	157/211 (74.4%)	165/214 (77.1%)	
If yes, strength			
1-2	136/153 (88.9%)	135/159 (84.9%)	
3	15/153 (9.8%)	23/159 (14.5%)	
4 (strongest)	2/153 (1.3%)	1/159 (0.6%)	
If yes, compliance			
Not compliant	7/152 (4.6%)	7/150 (4.7%)	
Intermittent	59/152 (38.8%)	63/150 (42.0%)	
Nearly daily	35/152 (23.0%)	32/150 (21.3%)	
Daily	51/152 (33.6%)	48/150 (32.0%)	
	Controls	Spa treatment	P
6 months			
Compression therapy	157/193 (81.3%)	150/190 (78.9%)	.556
If yes, compliance			.526
Not compliant	7/150 (4.7%)	3/142 (2.1%)	
Intermittent	46/150 (30.7%)	38/142 (26.8%)	
Nearly daily	33/150 (22.0%)	33/142 (23.2%)	
Daily	64/150 (42.7%)	68/142 (47.9%)	
12 months			
Compression therapy	131/184 (71.2%)	142/185 (76.8%)	.223
If yes, compliance			.627
Not compliant	7/128 (5.5%)	4/139 (2.9%)	
Intermittent	39/128 (30.5%)	45/139 (32.4%)	
Nearly daily	30/128 (23.4%)	28/139 (20.1%)	
Daily	52/128 (40.6%)	62/139 (44.6%)	