Chronic Venous Insufficiency: Worldwide Results of the RELIEF Study

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Chronic venous insufficiency (CVI) results in considerable morbidity and may seriously affect patients' quality of life. The RELIEF (Reflux assEssment and quaLity of lIfe improvEment with micronized Flavonoids) Study was a prospective controlled study designed to assess differences in the severity and in the evolution of symptoms and signs of CVI according to presence or not of venous reflux. Patients were thus separated into 2 comparative groups: those presenting venous reflux and those without venous reflux. The design of the study was multicentric and international, carried out in 23 countries over 2 years, in which 5,052 symptomatic patients assigned to classes C0 to C4 (on the basis of CEAP clinical classification) were enrolled. Patients were treated with micronized purified flavonoid fraction (MPFF*), consisting of 450 mg of micronized diosmin and 50 mg of flavonoids expressed in hesperidin over 6 months. In order to document changes in the quality of life of these patients during MPFF treatment, a new validated Quality of Life Questionnaire specific to CVI (CIVIQ) was used. The study also set out to gather epidemiologic data including the prevalence of venous reflux in symptomatic patients.

The RELIEF study provided important information about the epidemiology and clinical manifestations of CVI. Of particular interest was the observation that venous reflux was found to be absent in 57% of patients diagnosed as suffering from CVI belonging to CEAP classes C0 to C4. A positive relationship between symptoms of CVI (pain, leg heaviness, sensation of swelling, and cramps) and presence of venous reflux was found in the RELIEF study: symptoms were more frequent and more severe at presentation in patients with venous reflux. Moreover, during MPFF treatment, all symptoms showed a greater decrease in the group without venous reflux compared with the other group. This difference in the evolution of symptoms between the 2 groups was significant for pain, sensation of swelling, and cramps. Regarding leg heaviness and signs such as edema (assessed by leg circumference), patients improved equally independently of the presence or not of venous reflux. The significant and progressive improve-

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ment in the signs of CVI was reflected in significant changes in the clinical class of the CEAP classification, ie, from more severe to less severe stages. Continuous clinical improvement was found throughout the study and after treatment with MPFF for 6 months, the clinical scores of all symptoms and signs had significantly decreased ($p = 0.0001$ versus D0) in both groups. This improvement was also associated with a significant and continuous progression in the quality of life scores of all patients.

Age of patients, average time since diagnosis, and presence of venous reflux increased with the severity of the disease. The relationship shown in this study between these parameters and clinical CEAP classification reflects the progressive nature of CVI. Despite obvious symptoms of CVI, a very low percentage (21.8%) of the "intention-to-treat" (ITT) population had previously been treated. This was the case whether venous reflux was present or not.

*Daflon 500 mg, Alvenor, Ardium, Arvenum 500, Capiven, Detralex, Elatec, Variton, Venitrol.

Introduction

Chronic venous insufficiency (CVI), with its symptoms (pain, heaviness, sensation of swelling, and cramps) and clinical signs (edema and skin changes), is associated with a significant socioeconomic cost owing to its high prevalence, cost of investigation and treatment, and loss of working days.[1,2] The prevalence of varicose veins in Western adult populations is estimated at 25% to 33% of women and 10% to 20% of men.[3-5] The prevalence of edema and skin changes such as hyperpigmentation and eczema due to CVI varies between 3% and 11%.[6,7] The annual cost has been estimated to be 1 billion USD[8,9] and to account for 1.5% to 2% of the total public health care budget in European countries.[10] Data from the Brazilian Ministry of Social Welfare showed that CVI is the 14th most frequently quoted disease for loss of working days.[11] The chronic macrocirculatory and microcirculatory changes may lead to the most severe manifestation of CVI: a venous leg ulcer. This occurs in 1% of the population and increases consistently with age.[12,13]

From a pathophysiological point of view, there is no controversy over the fact that venous reflux, whether superficial or deep, is linked to venous hypertension, and thus to the clinical manifestations of CVI. Some studies have shown increasing prevalence of venous reflux with progression of the clinical stages of CVI.[14-17] However, there have been few data on the prevalence of venous reflux in patients with CVI until now.[18]

Today, in many countries, phlebotropic drugs are widely prescribed in CVI. Their usefulness has been demonstrated in terms of clinical efficacy in improving symptoms and signs of CVI. To date, no large study has been performed that confirms clinical efficacy in a large population encompassing a wide variety of different countries and cultures. Very little research[19] has been carried out to establish a relationship between severity of symptoms and signs of venous disease and presence of reflux. The role of venous reflux in the evolution of venous symptomatology during treatment is unknown. Micronized purified flavonoid fraction (MPFF), consisting of 450 mg of micronized diosmin and 50 mg of flavonoids expressed in hesperidin per tablet, has been shown to improve venous elasticity,[20,21] increase venous tone,[22,23] reinforce capillary resistance,[24] protect the microcirculation,[25,26] and increase lymph drainage.[27-29] Micronization is a well-established technique that allows better control of the dissolution process and a higher absorption of the active compounds from the human gastrointestinal tract[30,31] and therefore reduces interindividual pharmacokinetic variations. Clinical symptoms and signs of CVI (pain, heaviness, sensation of swelling, cramps, leg edema) as well as the more severe manifestation (skin changes and leg ulcers) have been shown to be significantly improved with MPFF treatment in various clinical studies.[32-37]

Quality of life of patients suffering from CVI is often extremely impaired.[38,39] The first quality of life (QoL) scale specific to CVI was developed and validated in France by Launois.[40-42] Assessment relies on a specific questionnaire known as CIVIQ (ChronIc Venous Insufficiency Questionnaire). It has been developed specifically in the field of CVI, where the main domains of impairment have

been clearly identified and focused on 4 quality of life dimensions: psychological, pain, physical dimension, and social functioning.[41,42]

The principal aims of the RELIEF study were as follows:

- to investigate differences in the evolution of symptoms and signs (heaviness, pain, cramps, sensation of swelling, edema) in patients suffering from CVI, according to the presence or not of venous reflux, and treated with MPFF 1,000 mg daily for 6 months
- to perform the psychometric validation of the multilingual multicultural versions of CIVIQ and to assess the evolution of quality of life (QoL) after treatment in both groups of patients (with and without venous reflux) suffering from CVI
- to collect international epidemiologic data on CVI and more particularly on venous reflux assessed with a pocket Doppler and photoplethysmography

Materials and Methods

The study was a prospective, multicenter, international study carried out in 23 countries over 2 years, and a controlled one in order to assess differences in the severity and in the evolution of symptoms and signs of CVI during MPFF treatment according to presence or not of venous reflux. Symptomatic patients, diagnosed by the examining physician on the basis of the symptoms and signs as suffering from CVI (CEAP clinical classes C0 to C4),[43] aged over 18 years, male or female, of any race, judged to be psychologically stable and motivated, whether or not wearing compression stockings, were enrolled in the study. Excluded were patients with concomitant active disease, any history of venous surgery, or assessed as CEAP clinical classes C5 or C6. Also excluded were immobilized, pregnant, or breastfeeding patients.

All patients were screened for venous reflux[44-47] by pocket-Doppler, the examining physicians having undertaken training with this technique. If venous reflux was detected, further examination was performed by photoplethysmography (PPG) to confirm and classify it as superficial and/or deep. After a washout period of 15 days, patients were separated into 2 groups: those presenting with venous reflux and those without venous reflux. All patients, whether with or without reflux, were treated with MPFF (1,000 mg daily) for 6 months and were instructed not to change their habits as to the wearing or not of compression stockings throughout the study period.

Checkup visits were scheduled every 2 months. The following parameters were assessed at each visit:

1. Symptoms (sensation of swelling, cramps, and leg heaviness) by using a 4-point scale (0 = absent, 1 = mild, 2 = significant, 3 = severe).
2. Pain by using a 10 cm visual analog scale (VAS).[48,49] The scale went from 0 (no pain) to 10 cm (intolerable pain).
3. Edema was assessed by measuring leg circumference in cm, using the Leg-O-Meter®. This device takes into account the height at which the measurement is taken, which greatly increases the precision and the reproducibility of measurement.[50-52]
4. Severity of the disease by using the CEAP clinical classification.[43]
5. Quality of life, by using the CIVIQ.[42] Patients were asked to fill out the self-administered questionnaire, made up of 20 questions. A total of 3,656 patients had 5 exploitable QoL assessments each and were included in the QoL evaluation. CIVIQ scores went from 0 for minimum score (reflecting a very poor QoL) to 100 for optimal score (reflecting a very good QoL).

The CIVIQ was validated in 6 different languages and translated into others.

The Lincoln Society was responsible for the consolidated statistical analysis of clinical data. The quality of life analysis was performed by 2 independent companies: ARCOS (Paris) and MAPI (Lyon). Clinical data analysis was obtained by using Kendall's Tan Test, Quade's test, and one-way analysis of variance with repeated measurements.[53-55]

Results

Study Population

Data were gathered from patients in 23 countries from the European, African, American, and

Asian continents. A total of 5,052 patients were screened. The intention-to-treat (ITT) population consisted of 4,527 subjects who had received 1,000 mg of MPFF during the study. The per-protocol population numbered 3,174 (patients who completed the study without protocol deviation).

Prevalence of Venous Reflux

Venous reflux was absent in 57% of patients assessed on Doppler examination. When present (43%), the venous reflux involved the long saphenous vein in 53%, the short saphenous vein in 14.3%, and both superficial veins in 32.7% of patients. Only those found to have reflux on the Doppler test went on to photoplethysmography (PPG). When reflux was confirmed (69%), superficial venous reflux alone was present in 55% and in 45% it was associated with deep venous reflux. Both groups ("with" and "without" reflux) were compared throughout the study.

Characteristics of CVI Patients

The sex ratio (female/male) in the total population was 4/1 and the mean age was 45.2 years. The age of the patients was significantly higher ($p = 0.03$) when venous reflux was present (47.2 years versus 43.8 years). A higher clinical CEAP class correlated with increased age of patients: the mean age of patients recorded in C0 (symptomatic) was 40.3 years, while in C4, it was 54.2 years.

The large majority of patients (63%) was professionally active but there were significantly fewer in the group with venous reflux: (61% vs 64.6%; $p = 0.01$). The group without venous reflux was characterized by more "white collar" professions (31.7% vs 28.7%; $p = 0.001$) and fewer "blue collar" professions (10.2% vs 15.6%; $p = 0.001$). A family history of venous disease was revealed in 61.5% of the total population and was significantly more common in the group with venous reflux (67% versus 58%; $p = 0.001$). CVI had been present for 7 years on average in C0 (symptomatic patients) and for 18.5 years in C4 patients.

Regarding symptoms of CVI at D0, sensation of swelling of either severity was significantly more often present in the group with venous reflux (83% of patients with and 75.4% of those without reflux, $p = 0.009$), and higher scores of pain were reported from the group with reflux (reading on the VAS scale: 3.9 cm for patients with vs 3.6 cm for those without reflux, $p < 0.001$). The relationship between leg heaviness and cramps and venous reflux was dependent on the severity of the symptom. In examining the total population suffering from leg heaviness and cramps, there was no relationship to the presence of reflux. However, considering serious symptom scores (graded 2 and 3 on the 4-point scale) in isolation, it was found that there was a direct relationship with the presence of reflux: 39% of patients vs 26% without reflux had "serious" scores of leg heaviness ($p < 0.001$), and 33% vs 29% ($p = 0.003$) had severe cramps.

Considering signs of CVI at D0, edema was more often present in the group with reflux (56% in the group with vs 43% in the group without reflux) although no significant difference in the

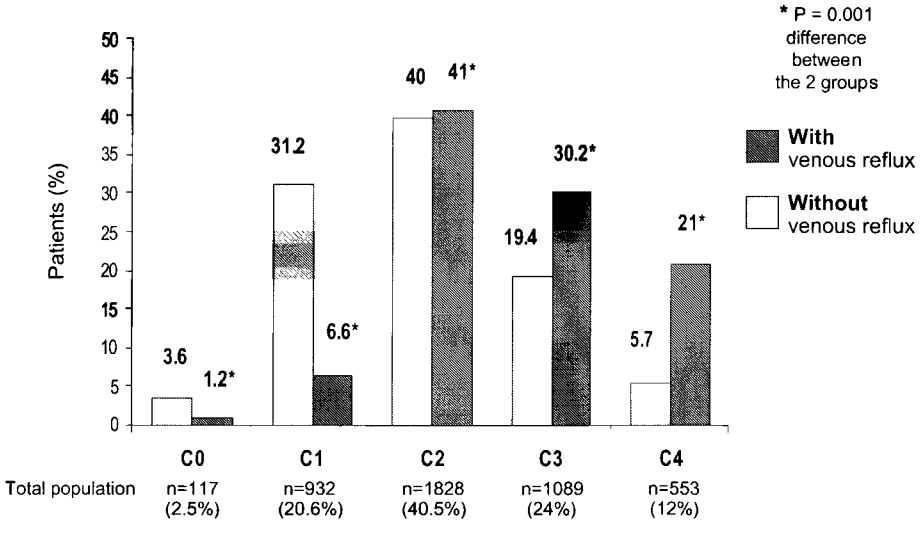

Figure 1.
Distribution of patients in CEAP clinical classes at D0. Columns in light grey represent percent of patients without venous reflux, and in dark grey, percent with reflux.

mean ankle perimeter was shown between the 2 groups (27.7 cm for patients with vs 27.1 cm for those without reflux, $p = 0.13$).

The difference between the 2 groups at baseline was also reflected in the severity of the disease, according to the CEAP clinical classification. Severity of the disease was more marked in the group with venous reflux: 60% of patients in C3 and C4 had reflux, while only 14% in C0 and C1. The difference in the distribution of participants in the clinical classes of the CEAP classification between the 2 groups was significant ($p = 0.001$). It is to be highlighted that most of patients were in C2 (40% of the total population), with a similar proportion in either group (Figure 1).

The distribution of QoL scores at baseline was different depending on the group (with or without reflux) with highly statistically significant levels ($p = 0.0001$). For Global Index Scores (GIS), patients with venous reflux had lower scores than patients without reflux, reflecting a poorer quality of life (62.2 versus 66.7, $p = 0.0001$). This was observed, not only for the GIS but also for all dimensions of the CIVIQ (psychological, pain, physical, and social). The subgroup with both short and long saphenous veins involved had significantly lower QoL scores, and so a poorer QoL, than the subgroups with isolated reflux of the short saphenous vein or of the long saphenous vein only (GIS = 59.3 versus 64.1 and 64.7 respectively, $p = 0.0001$).

Before entering the RELIEF Study, only 21.8% of patients had been treated for CVI (26.1% of the group with venous reflux and 18.5% of the group without venous reflux).

Clinical Outcomes of Symptoms and Signs

Leg heaviness was the most frequently reported symptom and was present in 94% of the RELIEF population. With MPFF treatment, 53% in the group without venous reflux had complete relief of leg heaviness against 37% in the other group. The difference in the evolution between the 2 groups did not reach statistical significance. The reduction in the clinical scores between D0 and the last observation was highly significant for each group and the whole population ($p = 0.0001$).

Regarding the evolution in clinical scores of sensation of swelling between the 2 groups, a significantly greater decrease was seen in the group without reflux: 47% in this group had complete relief of sensation of swelling against 34% in the group with venous reflux ($p = 0.007$). After treatment, more than 90% of patients in each group were relieved from sensation of swelling. The change between D0 and the last observation was highly significant for each group and the whole population ($p = 0.0001$).

A higher decrease in the cramps scores was seen in the group without reflux over treatment. The difference in the evolution between the 2 groups was significant: 53% in the group without venous reflux had complete relief of cramps against 45% in the other group ($p < 0.001$). The change between D0 and the last observation was highly significant for each group and the whole population ($p = 0.0001$). For pain, a significant difference was also shown for the evolution of the pain between the 2 groups ($p = 0.0001$) with greater improvement in the group without reflux. Over the 180 days of the study, the mean reading for patients without venous reflux decreased from 3.6 to 1.1 cm. For patients with venous reflux, the reading decreased from 3.9 to 1.5 cm. This decrease in pain was parallel and highly significant in each group of patients at the end of the study and in the whole population ($p = 0.0001$ versus D0).

For edema, no significant difference in the reduction in mean ankle perimeter between the group with venous reflux and those without venous reflux was observed during MPFF treatment (–1.2 cm in patients "with" and –1.1 cm in patients "without" reflux). The difference between the last observation and D0 was highly significant for each group and the whole population ($p = 0.0001$).

Sensitivity Analysis

The changes over time were evaluated by using a one-way analysis of variance with repeated measurements at each time of visit. Only fully documented patients (per-protocol population: 3,174 patients) were taken into account in this analysis (Table I).

Changes in CEAP Classification

At the end of the study, following 6 months of treatment with MPFF, there was a significant reduction in the number of patients (501 patients) in the more severe classes of the clinical CEAP classification (C3–C4), to the benefit of those in the less severe stages of the disease: C0, C1, C2 (Figures 2 and 3). These changes were found in both groups of patients (those "with" and those "without" reflux, $p = 0.0001$ vs D0), with a higher improvement in the clinical classes of CVI in pa-

Table I. Evolution of symptoms, signs and CEAP classification in the per-protocol population (n = 3,174).

		Ankle Perimeter, cm	Pain, cm	Swelling Sensation, % Patients	Leg Heaviness, % Patients	Cramps, % Patients	C0–C1–C2, % Patients	C3–C4, % Patients
D0	Without reflux	27.11	3.59	76.7	95.9	72.3	74.5	25.5
	With reflux	27.72	3.89	83.71	94.4	71.2	47.5	52.5
D60	Without reflux	26.68	2.44	64.0	83.5	42.7	77.1	22.9
	With reflux	27.19	2.72	72.7	84.2	51.3	51.7	48.3
D60 vs D0	Without reflux	Δ = (–0.43)	Δ = (–1.15)	p<0.001	p<0.001	p<0.001	**NS**	
	With reflux	Δ = (–0.53)	Δ = (–1.17)	p<0.001	p<0.001	p<0.001	**NS**	
D120	Without reflux	26.30	1.69	50.6	62.0	26.1	80.6	19.4
	With reflux	26.78	1.94	62.0	70.4	36.3	57.4	42.6
D120 vs D0	Without reflux	Δ = (–0.81)	Δ = (–1.90)	p<0.001	p<0.001	p<0.001	p<0.001	
	With reflux	Δ = (–0.94)	Δ = (–1.95)	p<0.001	p<0.001	p<0.001	p<0.001	
D180	Without reflux	25.96	1.12	28.3	40.6	15.1	83.6	16.4
	With reflux	26.54	1.43	47.7	55.8	23.3	60.6	39.4
D180 vs D0	Without reflux	Δ = (–1.15) p = 0.007	Δ = (–2.47)	p<0.001	p<0.001	p<0.001	p<0.001	
	With reflux	Δ = (–1.18) p = 0.012	Δ = (–2.46)	p<0.001	p<0.001	p<0.001	p<0.001	

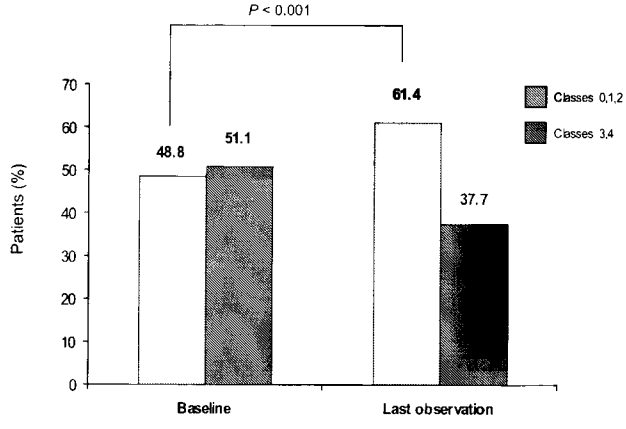

Figure 2. Changes in CEAP clinical classification in patients *with* venous reflux, at baseline and after treatment with MPFF. Columns in light grey represent patients in classes 0, 1, and 2 (less severe), and in dark grey, patients in classes 3 and 4 (more severe).

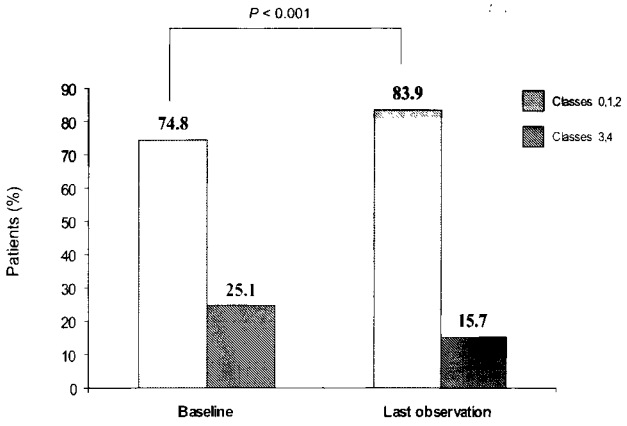

Figure 3. Changes in CEAP clinical classification in patients *without* venous reflux, at baseline and after treatment with MPFF. Columns in light grey represent patients in classes 0, 1, and 2 (less severe), and in dark grey, patients in classes 3 and 4 (more severe).

tients with venous reflux ($p < 0.001$): 13% of patients with venous reflux and 9% of those without reflux had changed from C3–C4 to C0, C1, C2.

More precisely, for all patients analyzed, the number in C3 (presence of edema) was considerably decreased (–427 patients) and the number with a clinical stage equal to 0 increased (+411 patients). These changes were highlighted in the group with venous reflux, which was overrepresented in C3 and C4.

Quality of Life Assessment

The acceptability of CIVIQ was indicated by the high rate of response at each assessment times.

Quality of Life Results

In both groups of patients, the global index improved continuously from D0 to the further assessment points. The main improvement in QoL was noted after 2 months (mean progression of 8.5) in the Global Index score (GIS) but further improvements were noted after 4 months (additional mean progression of 5.0 in the GIS) and after 6 months (additional mean progression of 4.0 in the GIS). Over the study period, a parallel progression in the GIS was observed in both groups, those without reflux having a constantly better QoL than the other group. Changes between D0 and D180 achieved statistical significance in all dimensions as well as in the global index, with p values equal to 0.0001 (Figure 4).

Changes in QoL scores between baseline and the end point were similar according to the group ($p > 0.0125$), except for pain dimension ($p = 0.005$). For that dimension, patients without venous reflux found their QoL slightly more improved than patients with venous reflux. This improvement in the quality of life was paralleled by the clinical improvement.

Psychometric Properties of CIVIQ

To evaluate the psychometric properties of the CIVIQ, 4 criteria had to be fulfilled: high precision, good construct, clinical validity, and responsiveness.

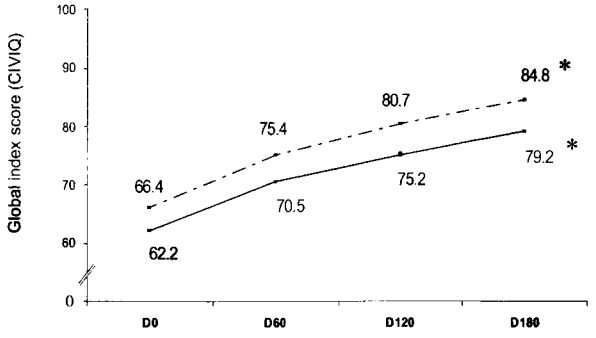

Figure 4. Changes in quality of life by global index (GIS) assessed by CIVIQ, in patients with (——) and without (- - -) venous reflux after treatment with MPFF. Higher scores of the CIVIQ mean better quality of life.
*$p = 0.0001$.

Precision of the instrument was good since all Cronbach's α coefficients were over 0.70. All intraclass correlation coefficients were higher than 0.80 over the washout period, whatever the clinical criteria chosen for the definition of clinically stable patients between D-15 and D0. The construct validity was satisfactory: all the item-scale correlations were higher than 0.4. A few items only in the social dimension need to be stabilized. The good clinical validity of CIVIQ has been confirmed: when stratification of the population at D0 was made, according to the CEAP classification from C0 to C4, all the dimensions of the CIVIQ scale were found to be significantly different with the severity of illness ($p = 0.0001$). The distribution of QoL scores was statistically different according to the symptom severity for all symptoms ($p = 0.0001$). QoL also significantly differed between the group with and without venous reflux ($p = 0.0001$). Responsiveness of the CIVIQ was demonstrated for improved patients in all dimensions and in the global index, irrespective of the various clinical criteria defined for assessing patients as improved. These changes achieved highly statistical significance ($p = 0.0001$). The effect size ratios were all lower than 0.40.

Evaluation of the Overall Efficacy of Treatment

Following treatment for 6 months, 79% of patients and 83% of investigators considered the effectiveness of MPFF as good or excellent. The evaluation was better within the group without reflux (82% of patients and 85% of investigators). With respect to overall acceptability, this was judged as good or excellent by 91% of patients and 93% of investigators.

Discussion

In this large international multicultural study, venous reflux was found to be absent in 57% of patients assigned C0 to C4 of the CEAP classification, within the limits of sensitivity of a hand-held Doppler examination. In those with venous reflux, reflux was confirmed in 69% by means of photoplethysmography (PPG)* examination. Considering the multiplicity and eclectism of daily practice in the different participating countries, both devices were specially designed for this study. Compared to other diagnostic tools, such as duplex ultrasonography or air plethysmography, the diagnostic tools used in this study fulfilled 2 main criteria: simple to operate and easy to handle in daily practice. After receiving special training, general practitioners were provided a hand-held Doppler,* and specialists were provided PPG.* These results suggest that there is a high prevalence of CVI without detectable or permanent venous reflux. In this study, patients without venous reflux were mostly in the less severe stages of CVI. Reduction in vein wall elasticity has been suggested as playing a role in the development of varicose veins and to precede the onset of valve incompetence.[56]

Early work has suggested that veins from patients with varicosities are more distensible than those from patients with normal veins.[57] Further studies[58] suggest that changes that occur in the venous wall morphology of varicose veins might cause valve deterioration, and thus reflux. Others found that severe vein distension is sufficient to prevent valves from closing properly.[59] It remains to be determined whether symptoms are linked to these changes and if they could predict the appearance of reflux.

The main objective of the RELIEF study was not to provide additional proof of the efficacy of MPFF, which has already been well established in numerous studies,[20-37] but to analyze the influence of the presence of venous reflux on the epidemiologic, clinical, and quality-of-life parameters in patients suffering from CVI. For this reason, patients were not randomized with regard to MPFF treatment. With regard to the presence or absence of venous reflux and other characteristics, blinding of investigators was not performed; this could limit the validity of some of the data and requires further study.

A relationship between the presence of reflux and the severity of the disease (according to the clinical CEAP classification) was shown in the RELIEF study. This has been reported in a number of studies where venous reflux was quantified[15-19]: deterioration in the parameters measured was usually reported as progression in clinical stage. Nicolaides[17] has shown that increased ambulatory venous pressure corresponds to an increased incidence of ulceration. To date, the available data suggest that there is a strong association between the severity of CVI and the anatomic distribution and extent of the venous reflux, but controversies remain over the role of reflux in the superficial, deep, and perforator systems in the production of complications of CVI. It was not possible to investigate such an associa-

*Trade mark: Microdop® 8 for the hand-held pocket Doppler and Vasotest® for PPG, SonoMed France, 14, rue de Moronval, 28100 Dreux, France.

tion in the present study since the use of pocket-Doppler and PPG did not provide enough reliable information.

The age of patients in this study increased with the severity of the clinical changes. These findings are similar to those reported in previous studies.[18,46] In the Edinburgh general population,[19] there was a trend toward a higher prevalence of reflux in the older age groups. In a healthy population from the Basle study, free of varicose veins at baseline, 10% developed edema and 8% developed skin changes over an 11-year period.[2] In the population of schoolchildren of the Bochum study,[46] there was an increase in the prevalence of reflux as the age of the children increased at successive examinations.

The relationships shown in the RELIEF study among age, duration of the disease, presence of venous reflux, and CEAP classification points to the progressive nature of CVI, through the deleterious effects of venous reflux.

The patient population was relatively young (mean age 45.2 years) and the large majority was professionally active, frequently with a positive family history of CVI. The sex ratio was 4:1 (female:male), far more in favor of women compared with most epidemiologic studies, in which a lower ratio was reported.[13,19,60] This may be due to the fact that the RELIEF study was conducted in patients attending for health care. Despite obvious symptoms of CVI, a very low percentage (21.8%) of these patients had previously been treated. The reasons for this are probably underestimation of CVI and lack of care.

The greater prevalence of venous reflux in the "blue collar" professions compared with the "white collar" could be related to the more physical nature of the work carried out in the "blue collar" group. A recent survey of the general adult population in France[61] revealed that work conditions are harder in the group with lower limbs complaints.

At the initial presentation, symptoms of CVI were related to the presence of venous reflux: higher scores of leg heaviness, cramps, and pain were found in the group with venous reflux. A greater percentage of patients complaining of sensation of swelling had reflux. The RELIEF study is, to our knowledge, one of the rare works, with those of the Edinburgh group[19,62] and Isaacs,[63] attempting to establish if symptomatology usually encountered in CVI is of "venous" etiology. Our findings are not similar to those reported in the general population of Edinburgh where symptoms of CVI (heaviness, sensation of swelling, aching, restless legs, cramps, itching, and tingling) were poorly related to the presence of reflux on duplex ultrasound scanning.[19] In previous work of the same group,[62] there was a weak and inconsistent relationship between symptoms and varicose veins, whereas in the Isaacs study, subjects with vein disease were found to be very symptomatic compared with controls. In this latter study, symptoms of aching, heaviness, tiredness, itching, swollen ankles, cramps, restless legs, and throbbing correlated with the presence of both small vein and large vein disease. The predominance of the female population in the RELIEF study may have biased the results as there are gender differences in "venous" symptomatology. On the other hand, the fact that participants in the Edinburgh study were questioned on the presence or the absence of symptoms, without assessing their severity, may have masked these relationships.

As expected, a greater decrease in most of the clinical symptoms scores was seen over the 6-month treatment when reflux was absent (except for leg heaviness where statistical significance was not reached). The improvement in signs of CVI was reflected in the reduction of edema and also in the changes in patients' condition, assessed by CEAP classification. The measurement of edema is often considered to be the most objective way of assessing the efficacy of CVI treatment.[51] The improvement in edema was highlighted by a significant decrease in leg circumference, and this was so for patients with and without venous reflux. Regarding modifications in the distribution in CEAP clinical classes between D0 and D180, a number of patients changed significantly from the more severe to the less severe classes. Patients with venous reflux underwent higher changes than in the other group. This was mainly due to the overrepresentation of C3 in the group with reflux and related to the reduction in edema after treatment.

At the end of the study, the reduction in the clinical scores of all symptoms and signs between D0 and the last observation was highly significant for both groups. The greatest improvements were reported within the first 2 months of treatment, but continuous clinical improvement was found throughout the study. This is proof that long-term treatment with MPFF is useful for sustained relief of patients with CVI. The fact that MPFF was efficient in both types of patients, with and without reflux, demonstrates its ability to counteract the deleterious effects of venous reflux.

With regard to quality of life, the study demonstrated a continuous improvement in QoL of the patients throughout the study period. Through the Relief study, CIVIQ itself appears to be a reliable instrument of high precision, good construct and clinical validity, and good responsiveness to assess patients' response to therapy. It may have a place in clinical practice as well as in clinical trials. CIVIQ might be used either as a global index or as a multidimensional profile.

Conclusion

The RELIEF study has been a pioneering effort to collect epidemiologic and clinical data on CVI, from more than 23 countries. This study has also reported on the deteriorating QoL in CVI, particularly when venous reflux is present, and correlated with how improvement in symptoms and signs with MPFF treatment is associated with improvement in QoL of patients suffering from CVI. The RELIEF study supports the assumption that symptoms are related to venous disease. This was seen at presentation in the population with venous reflux who had higher symptoms scores, and during MPFF treatment in the group without reflux, who showed greater improvement. The clinical results of the RELIEF study further demonstrate the efficacy of MPFF treatment, which caused a great reduction in the symptoms and signs of CVI, independently of the presence of venous reflux, and was sustained in the long term. This was reflected in significant changes in the clinical class of the CEAP classification, and in continuous improvement in quality of life scores over the study period. The CEAP clinical classification has proved to be a good evaluation tool of the severity of the disease at presentation, and significant changes in the distribution of patients in the clinical CEAP classification were revealed after treatment with MPFF. Through the RELIEF study, CIVIQ has been validated in different countries and found to meet stringent psychometric criteria, including high precision, good construct and clinical validity, and good responsiveness. CIVIQ appears to be a sensitive and a clinically valid tool, which might be used either as a global index or as a multidimensional profile.

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