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A Randomized, Double-Blind Multicentre Clinical Trial Comparing the Efficacy of Calcium Dobesilate with Placebo in the Treatment of Chronic Venous Disease

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Objective. *To assess the efficacy of calcium dobesilate on the quality-of-life (QoL) of patients with chronic venous disease (CVD).*
Design. *Randomised, parallel, double blind, placebo-controlled clinical trial.*
Methods. *Patients were recruited from vascular surgery clinics and randomised to 500 mg capsules of calcium dobesilate twice a day for 3 months or placebo. The primary outcome measure was 'QoL after 3 months' treatment measured by the specific Chronic Insufficiency Venous International Questionnaire (CIVIQ). Secondary outcomes were QoL at 12 months and assessment of the CVD signs and symptoms. The principal analysis was undertaken on the intention-to-treat (ITT) data.*
Results. *Five hundred and nine patients were recruited (246 to calcium dobesilate and 263 to placebo). The analysis of the 'QoL after 3 months' showed no significant differences between groups ($p = 0.07$). For secondary outcomes, oedema and symptoms of CVD, there were no significant differences between groups. In a multi-factorial analysis, the 'QoL at 12 months' was better in the calcium dobesilate group than in placebo group ($p = 0.02$).*
Conclusions. *Treatment with calcium dobesilate was not found to be superior to placebo on the QoL of CVD patients. The sustained effect of calcium dobesilate observed after treatment should be confirmed in future studies.*

Keywords: Calcium dobesilate; Chronic venous disease; Chronic venous insufficiency; Clinical trial; Randomised; Controlled trial.

Introduction

Pharmacological treatment is often prescribed for Chronic Venous Disease (CVD) because surgery and sclerotherapy are not always indicated and compliance with compression treatments such as elastic stockings is frequently poor. Flavonoids, horse chestnut extract, pentoxifylline and other drugs have been found to achieve considerable relief of the symptoms of CVD.[1,2,3] An international consensus symposium in 2005 concluded that venoactive drugs are effective in the management of venous symptoms based on published clinical trials and the experience of experts. Calcium dobesilate was given a level A recommendation.[4] However, a more recent systematic review concludes that clinical trials which provide this evidence have limitations.[5]

Calcium dobesilate (2,5 dihydroxy-benzenesulfonate) is a synthetic drug to treat CVD. It acts on the endothelium of capillaries by blocking the hyperpermeability, inhibiting platelet aggregation[6] and increasing red cell flexibility; these mechanisms contribute to an oedema-protective effect.[7] Three meta-analyses[5,8,9] have suggested that calcium dobesilate has more efficacy than placebo relieving oedema and some CVD symptoms. Heterogeneity has been detected among the trials due to the differing criteria in patient selection, stage of the disease, dosage of calcium dobesilate used, and selection of primary

The Appendix lists the Chronic Venous Insufficiency Study Group, Advisory Committee, Monitoring and External Audit.
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and secondary outcomes.[5] Additionally, the follow-up periods in all studies were relatively short.[5] In none of the calcium dobesilate clinical trials published to date, has patient Quality-of-life (QoL) been measured with a specific and validated scale for CVD.

Given the limitations of previous trials, uncertainties about the efficacy of calcium dobesilate still remain. Therefore, we designed a large trial with a long follow-up, and more rigorous methodology which includes a measure of QoL as a primary endpoint.

Materials and Methods

Patients were recruited between June 2002 and April 2004, from vascular surgery clinics in 32 Spanish hospitals. The Ethics Committee at each centre and the Spanish Drugs Agency evaluated and approved the study protocol. Written informed consent was obtained from all patients.

The inclusion criteria were adults ($\geq$18 years of age) of either gender with CVD, CEAP clinical grades 1 to 6[10–12] and able to complete a QoL questionnaire. Exclusion criteria included chronic or acute diseases that limited compliance to the protocol, scheduled surgery or sclerotherapy in the coming calendar year, pregnant or lactating women, patients with allergies or known intolerance to the study medication, history of neutropoenia or leucopoenia, and a baseline serum leucocyte count under 3,500/ml.

All patients were examined clinically, and a blood analysis and duplex ultrasonography were performed at baseline in order to confirm the presence of CVD and to exclude other illness associated with leg oedema. For clinical consistency throughout the study, the limb with the more advanced disease at baseline was assessed.

The allocation to treatment was randomised, centralised and computer stratified in blocks of 10 patients, by Clinical CEAP classification and centre. One group was assigned to 500 mg capsules of oral calcium dobesilate twice a day for three months, and the other, to placebo (inactive capsules of identical appearance and weight) twice a day for the same period.

After the treatment period, patients were followed up for nine months, making the total study length one-year. Each patient was visited four times: visit 1 at baseline/pre-randomisation, visit 2 for treatment assignment and treatment initiation (15 days after), visit 3 at completion of treatment (3 months) and visit 4 for final visit, end of the study (12 months). All medication was given to the patient at visit 2 and counted for compliance at visit 3. Patients were considered compliant if the 80% or more of the medication was taken.

QoL was measured using the Spanish validated Chronic Insufficiency Venous International Questionnaire (CIVIQ)[13] and was evaluated at visits 2, 3, and 4. Each visit also included a evaluation applying the CEAP classification and measuring perimeter of the ankle joint by the Leg-O-Meter®[14] and a 100 mm Visual Analogue Scale (VAS) for the assessment of oedema and symptoms, respectively. Duplex ultrasonography was performed to identify venous obstruction or reflux and to confirm the clinical diagnosis of CVD but not to refute it. The superficial veins, deep veins and perforating veins were assessed for venous reflux. We considered that the normal valve closure time for all veins in the standing position was 0.5 second, and reflux was present if the duration of retrograde flow was longer than this.

Variables of study

The main outcome measure was the QoL after three months of treatment measured by the CIVIQ questionnaire. Secondary outcome measures were QoL at the end of follow-up period (12 months); CVD signs (oedema) and symptoms (pain, heaviness, cramps, swelling, venous claudication, itching); and tolerance and safety of the treatment.

Sample size

The estimated sample size was 253 patients per arm, calculated from the GRANMO 5.0 statistical program.[15] An improvement of 10 points was hypothesized for the active group as compared to the placebo group in the overall CIVIQ score, which ranges from 0 to 100 points. The approximation of the analysis was bilateral. The values for the calculation of probability errors type I and type II were set at 0.05 and 0.10 respectively. The percentage of patients that would withdraw from the study or who would be lost to follow-up was estimated at 25%.

Statistical analysis

The analysis of efficacy was made on an intention-to-treat (ITT) basis. Additionally, a 'per protocol' analysis was performed.

Patients' baseline characteristics were compared before treatment was started to assess similarity of the two groups.

The main outcome was the comparison between groups in the overall CIVIQ score after three months of treatment. The CIVIQ included twenty questions, each with a score of 0 to 5. It assessed four QoL

domains: physical, psychological and social limitations, and pain. Analysis was based on the overall scores for each domain of the QoL questionnaire. The scores for each domain were standardised according to the method adopted by J. Ware for SF36.[16] The overall score or total QoL was obtained by the arithmetic sum of all domains to obtain a result between 0% (best QoL) and 100% (worst QoL). In the ITT analysis, the last available data (if there was any) or the worst (if there was no final data point) CIVIQ score were assigned to the missing data point.

For the evolution of the CIVIQ score, two-way analysis of variance (ANOVA) was performed. The factors were group (calcium dobesilate, placebo), time (baseline, the end of 3 months of treatment) and interaction between them. QoL was also evaluated throughout the study, from baseline to the end of follow-up.

A multi-factor ANOVA was used to assess other factors that could influence symptoms or oedema in CVD. The factors were age, gender, use of elastic stockings, physical therapy, previous venous surgery, sclerotherapy, venous thrombosis or pulmonary thromboembolism, certain concomitant medications (diuretic, analgesics, non-anti-inflammatory steroids drugs, corticosteroids), and associated diseases (renal, hepatic, or cardiac insufficiency). The ANOVA were undertaken by the Generalised Linear Models (GLM) procedure.

The main outcome measure was the change in QoL following treatment and during following up in the entire group. At a later stage we considered that a series of 5 subgroup analyses of QoL might be informative. We considered the seasonal recruitment period, only patients with symptomatic CVD, only patients with CEAP 3, CEAP 4, 5 and 6 venous disease, and analysing by CIVIQ dimensions.

For some secondary outcomes (such as oedema, pain or cramps), a student t test or a chi-square test were used depending on the quantitative or categorical values. For quantitative values the mean and standard deviation (SD) were calculated. An intermediate analysis was performed with the first 250 patients to assess the safety profile of calcium dobesilate. The statistical package SPSSwin 11.5, SPSS Inc, Chicago, Ill. was used for all analysis.

Results

The study included 509 patients with CVD, 443 (87%) of whom were women and 66 (13%) men; 246 (48.3%) patients were assigned to calcium dobesilate and 263 (51.7%) to placebo. A total of 378 patients (74.3%) completed the follow-up with no differences between the two groups: 185 (75.2%) patients in the calcium dobesilate group and 193 (73.4%) in the placebo group ($P = 0.68$). One hundred and thirty-one (25.7%) patients withdrew from the clinical trial (Fig. 1). The principal causes of withdrawal were voluntary decision not to continue (45.8%), follow-up loss (13.7%), protocol deviation (11.5%) and concurrent pathologies (9.2%). At baseline, 95% of patients in the dobesilate group and 96% in the placebo group had some degree of disability related to CVD (Table 1). The distribution of the CEAP classification was similar in both groups and the most frequent were 29.1% of patients with CEAP 2 (varicose veins), 26.3% with CEAP 3 (oedema without skin changes), and 23.8% with CEAP 4 (chronic skin disorders) (Table 2). All patients with CEAP 1, 5 and 6 were symptomatic. The patients with CEAP 2, 3 and 4 were symptomatic in the 96.3%, 97.6% and 98.1% of cases, respectively. The clinical history was similar between groups, except for diabetes mellitus, prolonged standing, physical therapy and venous claudication that were more frequently seen in the placebo group. Chronic hepatitis was more frequent in the calcium dobesilate group (Table 3). Those clinical factors were included in the multifactorial analysis.

Patient QoL at baseline differed during winter and summer (47.0 and 48.2, respectively) compared to the spring and autumn (42.0 and 42.7, respectively) ($p = 0.045$). But the seasonal period of recruitment did not result in any difference in patient QoL when groups were compared at baseline ($p = 0.829$).

The ITT results for the main outcome, overall CIVIQ score after three months' treatment, showed

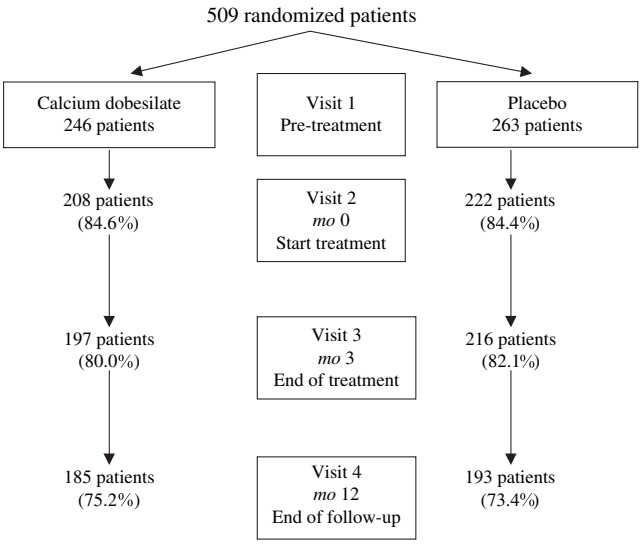


Fig. 1. Flow of patients in the clinical trial.

Table 1. Baseline Characteristics of Patients

		Calcium dobesilate	Placebo	*P*
		N = 246	*N* = 263	
Age (mean and SD)		53.3 (13.3)	54.7 (14.9)	0.27
Male/Female		29/217	37/226	0.51
CEAP Disability Score		*N* = 243	*N* = 259	
Asymptomatic		12 (4.9)	10 (3.9)	0.73
Symptomatic but functional without elastic support		164 (67.5)	185 (71.4)	
Symptomatic but functional with 8 *h* of elastic support		60 (24.7)	59 (22.8)	
Incapable of working		7 (2.9)	5 (1.9)	
Location of the reflux/obstruction by duplex ultrasound		*N* = 242	*N* = 253	
Obstruction	femoral	17 (7.0)	13 (5.1)	0.45
	popliteal	14 (5.8)	14 (5.8)	1.00
Reflux	popliteal vein above the saphenopopliteal junction	11 (4.5)	11 (4.3)	1.00
	popliteal vein under the saphenopopliteal junction	15 (6.2)	14 (5.5)	0.84
	internal saphenous	135 (55.8)	132 (52.2)	0.47
	external saphenous	26 (10.7)	33 (13.0)	0.48
	femoral vein above the saphenofemoral junction	18 (7.4)	18 (7.1)	1.00
	femoral vein under the saphenofemoral junction	19 (7.9)	18 (7.1)	0.86
	perforating veins	58 (24.0)	64 (25.3)	0.75

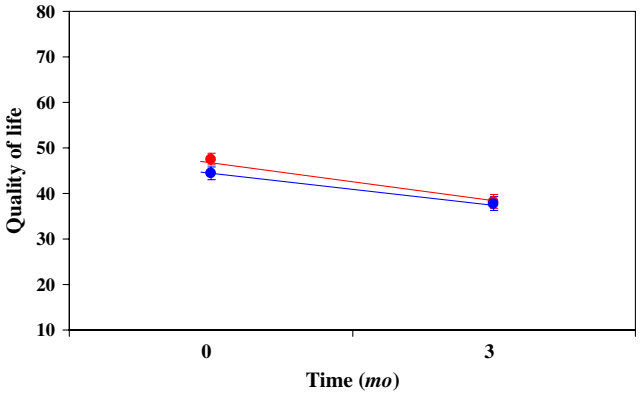
Table 2. CEAP at baseline

	Calcium dobesilate	Placebo	*P*
	N = 246	*N* = 263	
Value of clinical CEAP	*n* (%)	*n* (%)	
1 (Telangiectases, reticular veins)	35 (14.2)	37 (14.1)	0.47
2 (Varicose Veins)	61 (24.8)	87 (33.1)	
3 (Oedema with no skin changes)	70 (28.5)	64 (24.3)	
4a (Pigmentation, eczema)	28 (11.4)	35 (13.3)	
4b (Lipodermatosclerosis, white atrophy)	34 (13.8)	24 (9.1)	
5 (Healed Ulcer)	12 (4.9)	11 (4.2)	
6 (Active Ulcer)	6 (2.4)	5 (1.9)	
Anatomical alteration	*N* = 242	*N* = 252	
Superficial veins	203 (83.9)	217 (86.1)	0.52
Deep veins	36 (14.9)	30 (11.9)	0.35
Perforator veins	48 (19.8)	45 (17.5)	0.64
CVD Aetiology			
Primary	208 (86.0)	230 (91.3)	0.06
Secondary	26 (10.7)	20 (7.9)	0.35
Congenital	11 (4.5)	9 (3.6)	0.65
	n/N (%)	*n*/N (%)	
Venous Reflux by Eco-Doppler	151/246 (61.4)	165/263 (62.7)	0.78
Venous Obstruction by Eco-Doppler	16/253 (5.3)	17/242 (7,0)	0.85

Table 3. Clinical antecedents

	Calcium dobesilate *n*/*N* (%)	Placebo *n*/*N* (%)	*P*
Cardiac Insufficiency	7/234 (3.0)	12/256 (4.7)	0.35
Chronic Hepatitis	4/244 (1.6)	0/258 (0)	**0.05**
Chronic Renal Insufficiency	1/245 (0.4)	4/260 (1.5)	0.37
Compression bandage	8/231 (3.5)	7/242 (2.9)	0.79
Deep venous thrombosis	20/240 (8.3)	15/260 (5.8)	0.29
Diabetes Mellitus	6/244 (2.4)	23/260 (8.8)	**0.00**
Elastic compression	77/241 (31.9)	77/254 (30.3)	0.69
Physical therapy	12/244 (4.9)	25/256 (9.8)	**0.04**
Previous gestation	189/242 (78.0)	182/254 (71.6)	0.12
Prolonged Standing	187/245 (76.3)	217/260 (83.5)	**0.058**
Pulmonary Thromboembolism	3/243 (1.2)	5/256 (1.9)	0.72
Sclerotherapy	41/244 (16.8)	43/260 (16.5)	1.00
Superficial venous thrombosis	43/240 (17.9)	37/257 (14.3)	0.32
Venous Claudication	3/242 (1.2)	11/260 (4.2)	**0.05**
Venous surgery	61/245 (24.9)	57/261 (21.8)	0.46
Venous Ulcer	7/244 (2.9)	6/257 (2.3)	0.78
Venous Ulcer Recidivate	4/124 (3.2)	1/129 (0.8)	0.20

a significant overall improvement in both groups with no significant differences between groups ($P = 0.07$). The mean baseline CIVIQ score was 44.5 (22.4) in the dobesilate group and 47.5 (22.3) in the placebo group. At the end of the three-month period, the mean CIVIQ scores were 37.8 (22.6) and 38.2 (23.8), respectively. Overall, a significant reduction of 8 points (8%) was observed compared to the baseline value ($P = 0.001$) (Fig. 2).



	Basal (Visit2) *Mean (SE)*	3 *mo* (Visit3) *Mean (SE)*
Placebo (N=263)	47.5 (1.4)	38.2 (1.5)
Calcium dobesilate (N=246)	44.5 (1.4)	37.8 (1.4)

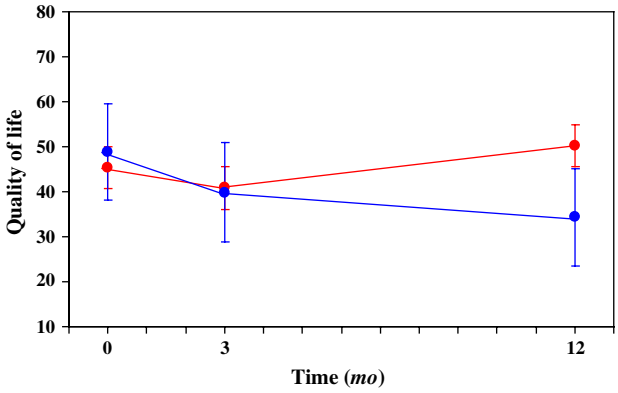
Fig. 2. Quality-of-life at three months of treatment. Evolution Visit2-Visit3: $P = 0.00$. Comparison between treatments Visit2-Visit3: $P = 0.07$.

The results of the overall CIVIQ score by subgroup analysis were similar to the principal analysis, and both groups were better in the overall score CIVIQ after three months' treatment, without any significant difference between them. The 'per protocol' analyses showed similar results.

The multi-factorial analysis of the overall CIVIQ score of the after three months' treatment showed no significant differences between groups ($P = 0.54$). Analysis of the QoL (measured by CIVIQ) at 12 months showed a significant difference in favour of the calcium dobesilate treated group ($P = 0.02$) (Fig. 3).

For oedema and CVD symptoms, both groups experienced a reduction in the mean malleolar perimeter after treatment of 3.3 mm ($P = 0.99$). Furthermore, the symptoms ameliorated in both groups, with a mean reduction VAS range of 9.0 mm to 13.2 mm. There were no significant differences between groups (Table 4).

Of the patients, who did not complete the study due to serious adverse events, three in the calcium dobesilate treated group were lost due to digestive intolerance (gastric pain, nausea and vomiting) and three in the placebo treated group were lost due to digestive intolerance, urticaria and Burkitt's Lymphoma. There were no cases of agranulocytosis or death during the study. No significant differences were found between groups in the number of patients with an adverse event (Table 5).



	Basal (Visit2) *Mean (SE)*	3 *mo* (Visit3) *Mean (SE)*	12 *mo* (Visit4) *Mean (SE)*
Placebo (N=251)	45.3 (4.6)	40.8 (4.8)	50.3 (4.7)
Calcium Dobesilate (N=240)	48.8 (10.7)	39.8 (11.0)	34.3 (10.7)

Fig. 3. Progression of quality-of-life score throughout the study. Multi-factor ANOVA. Evolution Visit2-Visit3-Visit4: $P = 0.37$. Comparison between treatments Visit2-Visit3-Visit4: $P = 0.02$.

Discussion

To date, clinical studies evaluating the efficacy of calcium dobesilate on CVD have focused on signs, symptoms or physiological parameters. In the present study we evaluated the efficacy of this drug in CVD by measuring the patients' QoL. This important clinical outcome was assessed using the CIVIQ questionnaire, a specific instrument that has been internationally validated.[13]

The number of patients recruited makes this study the largest randomized, placebo-controlled, double-blind calcium dobesilate clinical trial to date and the second largest with a drug for CVD. Furthermore, the follow-up was longer- nine months - than others similar clinical trials.

The general characteristics of the study sample are consistent with studies developed in Spain[17] and in others European countries.[18] Most of the recruited patients were middle-aged women with moderate CVD. It is important to mention that most of the patients were symptomatic and a high percentage had a history of prolonged standing. The CVD symptoms were reflected in the QoL score at baseline assessment and many participants presented some degree of functional limitation. Although patients were more symptomatic according to QoL measurements during winter and summer, the seasonal period of recruitment did not result differences between groups.

The patients in the calcium dobesilate group experienced a modest improvement after three months treatment, as suggested by a 7-point decrease (7%) from the baseline QoL score, but that was not statistically different from the improvement observed in the placebo group (9-point; 9%).

Initially, we anticipated a 25% withdrawal rate when designing the study, bearing in mind the long duration of the trial. The observed withdrawal rate was 26% and surprisingly the majority of withdrawals occurred during the recruitment period. The run in of the clinical trial coincided with the decision of the Spanish Drug Agency to remove CVD as an indication for calcium dobesilate treatment (http://www.hsanmillan.es/farma/flebotonicos.htm) because an unfavourable risk-benefits balance. This may have adversely affected recruitment to the study resulting in a long recruitment period.

Although patients were randomised and there was a similar percentage of withdrawals between groups, some baseline differences were detected. However, those factors did not have any influence in the main outcome results since the adjusted analyses did not modify the principal results.

Table 4. Comparison of signs and symptom score between groups – all data mean (standard deviation)

	Assigned Treatment (*n* patients)	Baseline Score Mean (*SD*)	Post-treatment Score Mean (*SD*)	*P*
Edema (*mm*)	Placebo (203)	270.1 (54.8)	266.8 (53.9)	0.99
	Calcium dobesilate (193)	258.2 (43.1)	254.9 (43.2)	
Symptoms (VAS; *mm*)				
Pain	Placebo (216)	50.3 (26.1)	37.8 (27.4)	0.55
	Calcium dobesilate (203)	48.8 (26.9)	37.8 (25.8)	
Swelling	Placebo (214)	50.7 (50.1)	37.5 (27.8)	0.38
	Calcium dobesilate (203)	45.8 (29.0)	36.2 (28.6)	
Heaviness	Placebo (214)	59.7 (25.5)	46.9 (28.8)	0.75
	Calcium dobesilate (203)	55.2 (27.3)	44.5 (28.4)	
Cramps	Placebo (211)	35.9 (31.5)	26.9 (28.7)	0.69
	Calcium Dobesilate (204)	34.3 (31.5)	24.1 (27.1)	
Venous Claudication	Placebo (213)	34.6 (30.4)	23.6 (26.2)	0.19
	Calcium dobesilate (205)	30.5 (29.7)	23.1 (27.4)	
Itching	Placebo (212)	42.2 (33.4)	31.3 (30.4)	0.40
	Calcium dobesilate (204)	42.4 (33.5)	35.9 (68.6)	

One of the main findings in this study is the beneficial effect observed in the placebo group at the end of three months' treatment in relation to the QoL. The therapeutic effect of placebo is well known, especially in treatment of pain.[19] Optimization of patient care during the study probably also contributed to the improvement in the placebo group. At least, this result shows the importance of including a placebo group in clinical trials to evaluate the drugs effects in CVD.

Several clinical studies have reported the efficacy of calcium dobesilate in oedema and in some symptoms related to chronic venous insufficiency.[20–25] Although our present results do not confirm these findings, it should be kept in mind that assessment of signs and symptoms of CVD was a secondary endpoint in our study. A recent clinical trial[24] evaluated oedema attributable to CVI and showed that calcium dobesilate was better than placebo. A 24% reduction in oedema volume was found in CVI patients. This study evaluated oedema by volumetric methods while our study measured the ankle circumference, a less precise measure. The drug dose was lower in our trial than in Labs[24] study so that a dose-dependent effect may explain the difference in findings. The reason for choosing a 1000 mg/day dose of calcium dobesilate in our trial was that previous studies had shown efficacy and that this dose was licensed for clinical use when the study was commenced.[21,22]

Table 5. Patients with adverse effects

	Calcium dobesilate $N = 246$	Placebo $N = 263$
	n (%)	*n* (%)
Total adverse events	46 (18.7)	45 (17.1)
Adverse events related to the medication	24 (9.7)	20 (7.6)
Withdrawal of treatment	12 (4.9)	11 (4.2)
Severe adverse effects	6 (2.4)	7 (2.7)
Severe adverse effects related to the medication	1 (0.4)	1 (0.4)

The adjusted analysis by factors that were considered able to influence the final results of the QoL at the end of three months' treatment demonstrated no differences between the two groups. However, at the nine-month follow-up we observed statistically significant differences in the progression of the QoL between the two groups that favoured the calcium dobesilate group. Thus after completing the treatment, the beneficial effect of calcium dobesilate remained or slightly increased over the nine-month follow-up, but the placebo group worsened by the end of the study with respect to baseline. These observations suggest the possibility of sustained therapeutic action of the calcium dobesilate in the CVD compared to placebo. Since this observation is based on a secondary analysis, a new clinical study would be needed to investigate this effect.

There was no significant difference in adverse events between the treatment groups. During the clinical study, no relevant adverse effects related to the calcium dobesilate were detected. Nevertheless, the study sample was not large enough nor the follow-up period long enough adequately to assess the safety of the medication with respect to agranulocytosis, an infrequent and severe adverse effect, observed in a case-population study.[26]

In conclusion, calcium dobesilate was as effective as placebo in improving the QoL of CVD patients at the end of three months' treatment. No significant differences in secondary outcomes were observed between the two groups. The sustained effect of improved QoL in the calcium dobesilate group after withdrawal of the drug should be studied in future trials and evaluated in patients with more advanced CVD.

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Disclosures

Before starting the trial, Laboratorios Dr. Esteve signed a written commitment to fully respect the researchers' independence and to allow the dissemination of results, whatever they could be.

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