Foam-Sclerotherapy, Surgery, Sclerotherapy, and Combined Treatment for Varicose Veins: A 10-Year, Prospective, Randomized, Controlled, Trial (VEDICO* Trial)

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The study compared, by a prospective, randomized method, 6 treatment options: A: Sclerotherapy; B: High-dose sclerotherapy; C: Multiple ligations; D: Stab avulsion; E: Foam-sclerotherapy; F: Surgery (ligation) followed by sclerotherapy. Results were analyzed 10 years after inclusion and initial treatment. Endpoints of the study were variations in ambulatory venous pressure (AVP), refilling time (RT), presence of duplex-reflux, and number of recurrent or new incompetent venous sites. The number of patients, limbs, and treated venous segments were comparable in the 6 treatment groups, also comparable for age and sex distribution. The occurrence of new varicose veins at 5 years varied from 34% for group F (surgery + sclero) and ligation (C) to 44% for the foam + sclero group (E) and 48% for group A (dose 1 sclero). At 10 years the occurrence of new veins varied from 37% in F to 56% in A. At inclusion AVP was comparable in the different groups. At 10 years the decrease in AVP and the increase in RT (indicating decrease in reflux), was generally comparable in the different groups. Also at 10 years the number of new points of major incompetence was comparable in all treatment groups. These results indicate that, when correctly performed, all treatments may be similarly effective. "Standard," low-dose sclerotherapy appears to be less effective than high-dose sclero and foam-sclerotherapy which may obtain, in selected subjects, results comparable to surgery.

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*VEDICO = venous disease control trial.

Introduction and Background

The treatment of varicose veins is still not standardized.[1-5] At the moment most treatments are not based on clear, evidence-based medicine, for large, homogeneous, randomized trials are not available. Hobbs' study, from St Mary's Hospital in London, comparing surgery and sclerotherapy, indicated that surgery is more effective on a long-term basis.[1] Stripping of the long saphenous vein is not used at present in many centers on the basis that selective ligation of incompetent sites is as effective as stripping, being less traumatic and costly and allowing short-stay surgery.[2-5] At the moment the combination of surgery and sclerotherapy is effectively used and appears to be very cost-effective. However, the best combination is not clear.[4-9] The preservation of the long saphenous vein (LSV) for bypass grafting, or to save the collateral circulation and prevent more serious complications in case of deep venous thrombosis (DVT), is generally possible when the vein is not severely varicosed or has not had complications such as episodes of thrombosis, phlebitis, or hemorrhage.[4-11] Ligation or section of the major sites of venous incompetence such as the saphenofemoral junction (SFJ) associated with sclerotherapy in the following months could be a good and cost-effective option.[9-14] Venous disease is chronic and requires chronic observation and treatment with regular reevaluation of patients.

Theoretically surgery of superficial veins should consider the following essential factors and elements[9-16]:

1. the combination of limited surgery, such as ligation or section of major incompetence sites, associated with follow-up treatment such as sclerotherapy or stab avulsion, is effective to control a chronic disease;
2. the cost of the treatment, which corrects a very common problem should be low;
3. the preservations of the long saphenous vein is an important option;
4. simplified surgery is an option to assess more carefully;
5. true recurrence of varices after surgery should be differentiated from the occurrence of new varices and evaluated in long-term, prospective studies.

The aim of this study was to compare, by a prospective, randomized method, 6 treatment options (Table I): A: "Standard" sclerotherapy; B: High-dose sclerotherapy; C: Multiple vein ligations; D: Stab avulsion; E: Foam-sclerotherapy; and F: Surgery (ligation associated with sclerotherapy). Results were analyzed 5 and 10 years after the inclusion and initial treatment.

Patients and Methods

Inclusion Criteria

After informed consent we included patients (age range 25–65 years) with uncomplicated (no

Table I. Age and sex distribution in the 6 treatment groups.

	Age, Years	Sex Males (%)
Sclero SDT		
A. Dose1	44.4, 3	**33**
B. Dose2	45, 5	**31**
Surgery		
C. Ligation	44, 7	**32**
D. Stab-avulsion	45, 5	**30**
Foam-sclero		
E. STD + foam J&J	42, 6	**31**
Combined		
F. Surgery + sclero2	42, 4	**32**
Stripping: nonrandomized reference group	43, 6	33

Sclero STD = sclerotherapy with STD (A. Dose1 indicates low dose and B. Dose2 indicates higher dose). Surgery is self-explanatory (2 groups treated either with ligation of the incompetent veins or with stab-avulsion). Foam-sclero indicates sclerotherapy with foam and combined treatment indicates the combination of surgery and high-dose sclerotherapy.

thrombosis/phlebitis, hemorrhage, or skin changes due to prolonged chronic venous insufficiency) primary varicose veins. Patients were randomized according to a random code into different groups. The code was opened after intervention had been decided.

Exclusion Criteria

Exclusion criteria were pregnancy, obesity, postthrombotic occlusion, and history of previous thrombosis, coagulation disorders, any cardiovascular or systemic disease requiring treatment, tumors, bone and joint problems, diabetes, and any possible cause of venous obstruction. Also patients with severe venous insufficiency, lipodermatosclerosis, and ulcerations were excluded. No patient was included in a period of 12 months after pregnancy.

Investigations

Patients were studied by color duplex scanning[4-6] and ambulatory venous pressure (AVP) measurements. Duplex scanning was performed with the patient standing. The venous system and the long saphenous vein (LSV) were assessed by high-resolution (10–13 MHz) probes (ATL 5000, Bothell, WA, USA).

Ambulatory venous pressure (AVP) was measured with a needle inserted into a vein of the foot. The patient, while standing, performed a 10-step exercise. The lowest pressure was defined as AVP (mm Hg) and the refilling time (RT, namely, the time needed for the venous system to reach again the initial pressure level) was measured in seconds. Previous work indicates that an AVP > 45 mm Hg and a refilling time faster than 18 seconds are associated with various degrees of venous incompetence. RT and, in some cases AVP, could be modified by the application of a thigh or below-knee tourniquet (inflated at 80 mm Hg) excluding the superficial venous system. When this occurred (with normalization of AVP and RT) the incompetence was considered to be associated with incompetence of the superficial system. The localization of the tourniquet indicated the level of incompetence (above or below knee). Therefore the possibility of improving the venous system by selective treatment (surgery and sclerotherapy of the superficial veins) of the incompetent venous sites was good. On the contrary, the persistence of an AVP higher than normal and of RT shorter than 18 seconds, even with the superficial system occluded, was considered to be a dynamic indication of deep venous incompetence, and therefore, the patient was excluded from this study.

Definition of Sites of Incompetence

A major site of incompetence[4,5] (which can be either incompetence of the saphenofemoral junction or incompetence of a perforating vein) was defined on the basis of the following:

1. Duplex scanning reflux (lasting more than 3 seconds with the patient standing)
2. Venous reflux that changed AVP or RT (more than 20% of their value). For example, an incompetent saphenofemoral junction that, with occlusion (by a tourniquet), decreased AVP from 55 to 45 mm Hg and increased and normalized RT from 13 to 19 seconds

All patients had incompetence of the long saphenous vein at the saphenofemoral junction associated with 1 or more incompetent venous sites (which could be defined as points of control or perforating veins). Patients with associated incompetence of the short saphenous vein were excluded. Surgeons expert in ultrasound tests and venous problems assessed all patients.

Interventions

The aim of surgery was to treat selectively all major points of incompetence in 1 surgical session. The minor incompetence sites were treated within 6 months after surgery with compression sclerotherapy.

Sclerotherapy: the methods used in this protocol were performed/applied as described in our previous work and publications.[4,5] Veins larger than 3 mm in diameter were treated with 1–2 mL injections of 3% sclerosing agent, veins between 2 and 3 mm, with 2% solution. Compression was used for 10–30 days after sclerotherapy on the basis of the dimension of the veins (3 mm in diameter or more: 3 weeks; 2 mm or less: 2 weeks). All treatments were performed in a period of 6 months.

High-dose sclerotherapy was used with the same indications and procedures of "standard" sclero, but the dosage of injected sclerosing agent was between 3 and 6 mL of 3% sclero-agent in

larger veins (> 3 mm in diameter). The idea behind high dose was that injecting more sclerosing agent into the vein produced a better displacement of blood and a higher level of vein wall inflammation and could be associated with a less prolonged period of compression (1–2 weeks for the larger veins).

Foam sclerotherapy: This original method, planned and devised by our group, uses a tensioactive substance (J&J-93FA). This product was originally produced to enhance ultrasound vision in arteries and veins (ultrasound contrast agent). The injection of J&J-93FA after the emulsioning process produces, owing to the fast decrease in superficial tension, enhancement from the presence of microbubbles (0.1 to 0.5 mm in diameter), which persist for 3–8 minutes in the venous circulation. Evaluation by (ventilatory + perfusional) lung scintigraphy (12 cases) indicated no perfusional defects after injection of 10 mL of foam. Transesophageal duplex (22 cases) also indicated that when arriving at the pulmonary circulation the foam was barely recognizable as a moderate enhancing of pulmonary arterial flow. The first-pass effect (after passing through the pulmonary circulation) completely dissolves the microfoam, which is not detectable in successive passages (3–5 minutes) (J&J-94FA Investigator Brochure, Cardiovascular Research, data on file). Ultrasound venous contrast agent (emulsions) have been developed to increase the visibility of vascular flow by increasing the ultrasound echo by diffusion of microbubbles or polymers. In 1,984 ultrasound contrasts with foaming, properties have been considered to produce foam when coupled with sclerosing agents.

Foam Sclerotherapy: Irvine Technique

Two 5–10 mL syringes are used. One syringe is coated with the foaming agent. The total quantity needed for coating is 0.1–0.2 mL. The second syringe is filled with the sclerosing agent (3%) and the 2 syringes are connected with 10 cm of standard infusion set tubing. The pumping of the sclerosing agent into the other syringe and the passage back to the sclerosing agent syringe can be achieved with the motion of 1 hand only. After only 5 passages between the 2 syringes a fine, persistent foam is obtained. The transparent infusion-set tubing is used to evaluate the foaming process. When no liquid is visible the foam is ready for injection.

Foam status time (FST) has been defined as the time needed for the foam to become completely liquid. As a minimal, residual part of the foam may require a long time to dissolve, the 50% FST or foam reduction time (FRT), measured in a vertical transparent column, is considered a better evaluation measurement of the stability of foam. With the Irvine method 50% of the foam becomes completely liquid in an average of 4 minutes. This number can be influenced by several factors including quantity of foaming agent and sclerosing agent, environmental temperature, velocity of passages between syringes and outlets, and type of syringes. This requires fast injection time (the veins should be injected within 2–3 minutes after the preparation of the foam. This process can be obtained with any sclerosing agent, and it is not related to a specific agent, for the foam mainly depends on the foaming agent and not on the tensioactive properties of the sclerosing agent.

Effects of foam: The foam completely displaces blood from the vein. This allows better contact with the vein wall, causing massive inflammation and, eventually, a nonthrombotic occlusion of the vein segment. This is also visible with ultrasound, which detects the foam dispersion in the venous system and the extension of foam to lateral branches. Minutes after the infusion the foam is still visible and its presence in collateral branches indicates that there is no need for other injections in these veins. Therefore, the method includes both the use of foam and injection under careful ultrasound guidance (ultrasound foam sclerotherapy or UFST).

Surgery

Flush ligation/section (group C) or stab avulsion (D) were performed under general (22%), spinal (44%), or local anesthesia (34%). Dexon sutures were used for vein ligation and Prolene was used for skin sutures. All patients went home the same day of the treatment. The difference between C and D was that, in group D, some segments of veins (2–5 cm) were removed, whereas in C, only selective ligation of the incompetent sites was performed. In this group ligation was done by the method of the "closed loop technique." This method avoids exposure of the endothelial surface to the subcutaneous tissue. The vein is exposed by a small skin incision. A segment of vein is exposed and cleaned by use of a Dechamps hook surrounding the vein for dissection. Veins are not opened. When a suitable distance/loop of vein is available, the vein is gently pulled out in a loop, ligated—when empty of blood—at the

basis of the loop, and replaced under the skin. This method was developed to avoid local neoangiogenesis due to the contact of the internal surface—resulting from section of the veins—with the tissues.

Endpoints of the study were the following: 1) variations in AVP, RT; 2) presence of duplex-reflux; 3) number of recurrent or new incompetent venous sites.

After surgery, patients were treated with a single weight-related dose of subcutaneous low-molecular-weight heparin (Clexane 100 mg per kg). One dose of a broad-spectrum cephalosporin was also administered within 1 hour before surgery. TED (Kendall, thromboembolic-deterrent) stockings were used for 10 days after surgery and after all sclerotherapy sessions. All sclerotherapy sessions (and sclero following surgery) were within a maximum period of 6 months and all surgical treatments were achieved within a period of 30 days (in case of repeated ligations). However, most surgical treatment (95%) were in a single session. No other treatments (excluding compression) were used in the follow-up period.

Follow-up: Patients were reevaluated and studied with duplex every year. Repeated sclerotherapy to control new varices was performed during the control session during the first 6 months of follow-up in the sclerotherapy groups. One to 3 injections were performed in these control-sessions. Sigvaris stockings (Ganzoni, Switzerland; 20–25 mm Hg at the ankle) were prescribed and used during the 10-year follow-up period by all patients.

Parallel comparison with stripping: Results obtained from a sample of a comparable (for clinical and hemodynamic data), parallel group of patients who underwent stripping were also included for comparison.

Note: Patients included into this study could have been defined as "ideal" candidates for sclerotherapy or stab-avulsion treatment and for stripping. They had no deep venous incompetence and no other vascular complications (obstruction, arteriovenous communications). Also, considering several factors, including the proximity to the treatment centers, the compliance of these subjects was particularly good. About 65% of patients were working in hospitals or in a medical environment or were medical staff or relatives of medical personnel.

Indications for surgery/treatment (present in all randomized patients) were cosmetic problems (large, visible veins), signs and symptoms (edema, heavier limbs, initial signs of chronic venous hypertension), and fear of complication (bleeding, thrombosis).

Statistics: Patients were evaluated with parametric and nonparametric tests (chi^2 and Mann-Whitney U-test for AVP and RT values and for comparing the number of new incompetent venous sites. Intention-to-treat analysis was used to evaluate the outcome of treatments. We defined as lost the patients not completing the follow-up at 10 years. Failures or exit points were considered as those patients who needed any new intervention (surgery or sclero) after 10 years. The total of ITT (intention-to-treat) subjects is the number including the failures plus the lost patients. The percentage of negative results (lost + failures) was obtained by considering as 100% the number of included subjects.

Results

The numbers of patients (Table I), limbs, and treated venous segments were comparable in the 6 treatment groups, which were also comparable for age and sex distribution.

The occurrence of new varicose veins at 5 years varied from 34% for group F (surgery + sclero) and ligation (C) to 44% for the foam + sclero group (E) and 48% for group A (dose 1 sclero). At 10 years the occurrence of new veins varied from 37% in F to 56% in A (Table II).

AVP: At inclusion AVP and RT were comparable in the different groups. At 10 years the decrease in AVP and the increase in refilling time (RT), indicating the decrease in venous reflux, were generally comparable in the different groups (Table III). Also the numbers of newly formed points of major incompetence were comparable in all treatment groups. The analysis of these results indicates that, when correctly performed, all treatments are effective in a comparable way. Repeated sclerotherapy appears to control signs and symptoms by controlling venous pressure and refilling time. The low-dose "standard" sclerotherapy is less effective than high-dose sclero and foam-sclero, which obtained comparable results with a more limited compression time. The parallel stripping group was comparable for age and sex distribution (Table I). The group included 140 patients (244 limbs with 211 venous segments treated—including the long saphenous vein). The occurrence of new veins was 39% at 5 years and 45% at 10. The sum of lost + failures in

Table II. Results: patients treated (included and completing the study) of vein segments sclerosed or treated with surgery with evaluation of the development of new veins not present at initial evaluation.

	Sclero Dose1	SDT Dose2	Surgery Ligation	Stab-avulsion	Sclero STD+ Foam J&J	Surgery+ Sclero2
Groups	A	B	C	D	E	F
Number InPats	148	136	**155**	144	150	**154**
CPats	123	112	**132**	122	129	**131**
Limbs	221	222	**239**	244	211	**234**
Segments	322	345	**335**	365	345	**354**
5y new veins	48	**41**	**34**	40	**44**	**34**
10y new veins	56	**49**	**38**	41	**51**	**37**
Lost patients	25	**24**	**23**	22	**21**	**23**
Failures	12	**9**	**14**	37	**10**	**8**
Total (ITT)	37	**33**	**37**	59	**31**	**31**
%	25	**24**	**23**	41	**20**	**20**

Sclero STD indicates sclerotherapy with STD (A. Dose1 indicates low dose and B. Dose2 indicates higher dose). Surgery: the 2 groups were treated either with ligation of the incompetent veins or with stab-avulsion). Foam J&J-sclerotherapy indicates sclerotherapy with foam and sclerosing agent and combined treatment indicates the combination of surgery and high-dose sclerotherapy.

InPats = included patients; Cpat: patients completing the study; Lost patients: patients not completing the follow-up; Failures: patients who needed a new intervention (surgery or sclero). Total ITT (intention to treat) is the number of the failures + lost patients and % is the percentage of negative results (lost + failures) considering 100% the number of included subjects. Pats = patients; 5y = >5 years follow-up; 10y = 10-year follow-up.

Treatments A to E all within 4 months; Treatment F: initial treatment + sclero within 6 months: Retreatment every year (2–8 sclero injections per leg).

Comparable stripping group: at 5 years the percent of limbs with new varicose veins was 39% and at 10 years it was 45%. Lost + failures in stripping were 54% (34% failures + 20% lost) ($p > 0.05$ in comparison with all other groups).

stripping was 54% (34% failures + 20% lost). This number was significantly larger ($p < 0.05$) in comparison with all other groups.

ITT (intention-to-treat) analysis. Considering failures (including dropouts), groups E and F had only 20% of failures. In group C there were 23% of failures (difference is not significant). In groups B and A there were 24% and 25% of failures ($p < 0.05$), and in group D, failures were equivalent to 41% of included patients ($p < 0.02$). The sum of lost + failures in stripping was 54% (34% failures + 20% lost). This percentage was higher, ($p > 0.05$) in comparison with all other groups. The definition of lost patients in venous disease may be misleading. They may fail to come back because they have no other problem or just because they have new problems and go to another center. We were able to get in touch with 87% of the dropouts, who declared that they were basically asymptomatic and not interested in being seen and evaluated again.

In the closed-loop ligation (C group) the occurrence of new veins, particularly in the area of loop ligations, was significantly lower than in the stab-avulsion group (this part of the study will be presented in a separate publication).

Comment on foam-sclero. This is the first long-term, randomized study on foam-sclero. The

Table III. Variation in duplex and AVP parameters in 10 years.

		Sclero		Surgery		Sclero Foam	Surg+ SC2	Differences Among Groups, p
		D1	D2	Lig	Stab-A			
Groups		A	B	C	D	E	F	
Base	AVP	54, 3	54, 4	55, 4	54, 4	56, 4	55, 6	ns
	RT	11, 3	10, 3	12, 4	11, 3	12, 3	12, 3	ns
	DPX	**6, 2**	**5, 3**	**5, 2**	**6, 2**	**5, 3**	**5, 3**	ns
10 Y	AVP	45, 4	44, 3	44, 6	43, 4	42, 3	44, 3	<0.05
	RT	19, 4	20, 2	21, 3	22, 4	19, 4	19, 3	<0.05
	DPX	**1, 1**	**1, 1**	**1, 1**	1, 0.5	1, 1	1, 0.5	<0.05

AVP is expressed in mm Hg; RT or refilling time, is expressed in seconds; duplex results (DPX) are expressed as the number of major sites of incompetence.

Sclero STD indicates sclerotherapy with STD (A. Dose1 indicates low dose and B. Dose2 indicates higher dose). Surgery is self-explanatory (2 groups treated either with ligation of the incompetent veins or with stab-avulsion). Foam J&J-sclerotherapy indicates sclerotherapy with foam and STD (sclerosing agent) and combined treatment indicates the combination of surgery and high-dose sclerotherapy (SC2 in this table).

method was originally developed in our units in 1986 on the basis of a technical idea of an Australian vascular surgeon, Michel Grigg, working and researching at St Mary's Hospital in London, under the supervision of Andrew Nicolaides. Foam-sclero is effective and safe, and it is a combination of ultrasound-guided treatment and sclerosing injection. The method, which is a surgical technique that should be used only by specialists, should be refined, for no standards are available, but this first controlled-randomized trial indicates the efficacy, simplicity, and flexibility of this method (this is also the subject of a separate report on this method, which is in publication).

Discussion

The first part of the VEDICO (Venous Disease Control) trial has indicated that, even in centers of excellence, basically there are no definite standards[2] for the treatment of varicose veins. There are national and regional variations in treatment[12,15] owing to several aspects including financial considerations and medical background. In the last 2 decades, saphenous vein-sparing surgery—its principles, techniques, results, and outpatient treatment—have become more widespread and known.[16] Repeated surgery for recurrent saphenofemoral incompetence is still a significant clinical problem,[17] both in primary venous incompetence and in the surgical management of varicose veins in more advanced chronic venous insufficiency.[18] In some centers it is believed that stripping of the long saphenous vein reduces more effectively than simple flush ligation the rate of reoperation for recurrent varicose veins.[18] Five-year results of a randomized trial[19] suggest that stripping, when associated with avulsion/ligation of collateral incompetent sites and with careful follow-up, could be effective. The combination of high saphenous ligation and sclerotherapy[4,5,20] is also effective and cost-effective. Stripping alone, without follow-up treatment (ie, sclerotherapy), rarely achieves full control of varicose veins in a single step. Complications of varicose vein surgery are usually limited.[21] However, simpler surgery may also reduce the number and frequency of complications. Superficial vein valve

repair with a new external valve support (EVS) is still in its initial phase.[22] This method used for conservative treatment is not always possible and more prolonged observation is needed. Finally[23,24] the evaluation of the effects of treatment in chronic venous diseases is not yet standardized, and we need randomized trials to evaluate the best therapeutic option for varicose veins. A recent study indicates that distal long-saphenous vein ligation may be as effective as flush ligation.[25] However, this study was retrospective and not randomized and no diagnostic or dynamic standard was used. Our SAFE-Junction study comparing flush ligation and distal long-saphenous ligation (4–5 cm from the saphenofemoral junction) indicates that there are no significant differences when both treatments are correctly performed.[26]

In the present study we used a combination of high-resolution color duplex and ambulatory venous pressure measurements to combine both morphologic and dynamic data. These methods of evaluation are not yet standardized or generally diffused. Particularly AVP and other dynamic tests (photoplethysmography) are mostly used for research applications. A quality-of-life evaluation should be included in studies of this kind, but no reliable method had been developed at the moment of the planning of the study, and even now there is no real method to evaluate the effects of venous disease on quality of life. The epidemiologic study at San Valentino[27] indicates that about 87% of subjects with chronic venous disease has no significant change in their quality of life and about 30% of subjects with venous disease did not perceive the problem as a significant one and did not require medical evaluation.

This prospective study indicates that several treatment methods can be effective in treating primary varicose veins. The different methods should be better evaluated comparing efficacy and costs—a cost-analysis report is under analysis—but it seems that different results may be obtained in different places. For instance sclerotherapy (with elastic compression following for days or weeks) is not a reasonable option in Hawaii or in places with hot climates (or, eg, in southern Italy in summer). While ligation/section of veins may achieve a 100% occlusion rate at 10 years, sclerotherapy may be associated with a 42% recanalization rate at 10 years or with the reopening, dilatation, or ex-novo formation of varicose venous branches. This may be not important in treating older patient (ie, the priority of avoiding complications such as ulcers, thrombosis, and bleeding can be achieved with a simple, complication-free, cheap injection). One of the major problems of these treatments—considering that they are very limited in costs—is that profits and reimbursements are very limited. In a world of evidence-based medicine—where evidence is exclusively collected in very expensive trials, concerning very expensive treatments, leading to high profits—nobody is really interested in evaluating treatments for venous diseases. Reimbursements and profits for venous diseases are low and trials or studies are organized only when profit is easy and can be shared (eg, subfascial endoscopic perforator surgery, radiofrequency, laser, or endovascular treatment). Therefore, real, prospective, randomized trials are almost impossible to organize. Considering the high costs and many difficulties in organizing a clinical study in this field, in the future a comparable, large, prospective trial (or registry) should be organized by a collaboration of several centers.

NOTES:

- There is no conflict of interest. The study was organized as an independent trial. No commercial sponsor was included in the study.
- The sclero agents used were commercially available.
- The foaming agent is not commercially available.
- We are very grateful to Dr. G. Goren and to Prof. B. Eklof.
- This study is in evolution into a registry. Researchers interested in contributing with their results can get in touch with the hub center (S. Valentino).

REFERENCES

1. Hobbs JT: Surgery and sclerotherapy in the treatment of varicose veins. A random trial. Arch Surg 109:793-796, 1974.
2. Belcaro G, Cesarone MR, Lebard C, et al: Resultat de

l'etude preliminare a l'enquete VEDICO. Angeiologie 23:67-68, 1999.

3. Rutherford RB, Sawyer JD, Joned DN: The fate of residual saphenous vein after partial removal or ligation. J Vasc Surg 12:422-426, 1990.
4. Belcaro G, Nicolaides AN, Veller M: Venous Disorders: A Manual of Diagnosis and Treatment. Cambridge: Saunders, 1996.
5. Belcaro G, Nicolaides AN, Stansby G: The Venous Clinic. London: Imperial College Press, 1999.
6. Belcaro G, Nicolaides AN: Noninvasive Investigations in Vascular Disease. London: Imperial College Press, 2000.
7. Bergan JJ, Yao JST: Surgery of the Veins. New York: Grune and Stratton, 1985.
8. Browse NL, Burnand KG, Lea Thomas M: Diseases of the Veins: Pathology, Diagnosis and Treatment. London: Arnold, 1976.
9. Tibbs DJ: Venous disorders, vascular malformations and chronic ulceration in the lower limbs. In: Oxford Textbook of Surgery, ed. by Morris PJ, Malt RA. Oxford: Oxford University Press, 1994, pp 503-596.
10. Sadick NS, Schanzer H: Combined high ligation and stab avulsion for varicose veins in an outpatient setting. Dermatol Surg 25:257, 1998.
11. Villaviciencio JL: New trends and operative techniques in the management of varicose veins. Hawaii Med J 59:249-252, 2000.
12. Galland RB, Whatling PJ, Crook TJ, et al: Regional variation in varicose vein operation in England. Ann R Coll Surg Engl 82:275-279, 2000.
13. Perrin MR, Guex JJ, Ruckley CV, et al: Recurrent varices after surgery (REVAS), a consensus document REVAS group. Cardiovasc Surg 8:233-245, 2000.
14. Tsavelas G, Ranaboldo CJ: Varicose veins made easy. Ann R Coll Surg Engl 82:120-121, 2000.
15. Lees TA, Beard JD, Ridler BM, et al: A survey of the current management of varicose veins by members of the Vascular Surgical Society. Ann R Coll Surg Engl 81:407-417, 1999.
16. Zamboni P, Marcellino MG, Cappelli M, et al: Saphenous vein sparing surgery: Principles, techniques and results. J Cardiovasc Surg 39:151-162, 1998.
17. Gibbs PJ, Foy DM, Darke SG: Reoperation for recurrent saphenofemoral incompetence: A prospective randomised trial using a reflected flap of pectineus fascia. Eur J Vasc Surg 18:494-498, 1999.
18. Cassina PC, Brunner U, Kessler W: Surgical management of varicose veins in advanced chronic venous insufficiency. Curr Probl Dermatol 27:174-181, 1999.
19. Dwerryhouse S, Davies B, Harradine K, et al: Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: Five year results of a randomised trial. J Vasc Surg 29:589-592, 1999.
20. Ishikawa M, Morimoto N, Sasajima T, et al: Treatment of primary varicose veins: An assessment of the combination of high saphenous ligation and sclerotherapy. Surg Today 28:732-735, 1998.
21. Critchley G, Handa A, Maw A, et al: Complications of varicose vein surgery. Ann R Coll Surg Engl 79:105-110, 1997.
22. Incandela L, Belcaro G, Nicolaides AN, et al: Superficial vein valve repair with a new external valve support (EVS). The IMES (International Multicenter EVS Study). Angiology 51:S39-52, 2000.
23. Neglen P, Raju S: Ambulatory venous pressure revisited. J Vasc Surg 31:1206-1213, 2000.
24. Nicolaides AN, Albenbalm L, Akeson H, et al: Investigation of chronic venous insufficiency. Circulation. 102:e126-163, 2000.
25. Dortu JA: Traitement des varices des membres inferieurs par la phlebectomie ambulatoire (methode de Muller). Technique, indications et resultats. Ann de Chirurgie 51:761-772, 1997.
26. Belcaro G, Nicolaides AN, Cesarone MR, et al: Flush ligation of the sapheno-femoral junction vs simple distal ligation. A randomized, 10-year follow-up. The Safe Study. Angeiologie 54;19-33, 2002.
27. Cesarone MR, Belcaro G, Nicolaides AN, et al: "Real" epidemiology of varicose veins and chronic venous diseases. The San Valentino vascular screening Project. Angeiologie 54:33-43, 2002.
28. Nicolaides AN, Belcaro G, Chan P: Chronic deep venous insufficiency. In: Haimovici's Vascular Surgery. New York: Blackwell Science, 1998, pp 1242-1258.