Endovenous therapies of lower extremity varicosities: A meta-analysis

Renate van den Bos, MD,[a] **Lidia Arends, PhD,**[b,c] **Michael Kockaert, MD,**[a]
Martino Neumann, MD, PhD,[a] and **Tamar Nijsten, MD, PhD,**[a] *Rotterdam, The Netherlands*

Background: **Minimally invasive techniques such as endovenous laser therapy, radiofrequency ablation, and ultrasound-guided foam sclerotherapy are widely used in the treatment of lower extremity varicosities. These therapies have not yet been compared with surgical ligation and stripping in large randomized clinical trials.**
Methods: **A systematic review of Medline, Cochrane Library, and Cinahl was performed to identify studies on the effectiveness of the four therapies up to February 2007. All clinical studies (open, noncomparative, and randomized clinical trials) that used ultrasound examination as an outcome measure were included. Because observational and randomized clinical trial data were included, both the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Quality Of Reporting Of Meta-analyses (QUORUM) guidelines were consulted. A random effects meta-analysis was performed, and subgroup analysis and meta-regression were done to explore sources of between-study variation.**
Results: **Of the 119 retrieved studies, 64 (53.8%) were eligible and assessed 12,320 limbs. Average follow-up was 32.2 months. After 3 years, the estimated pooled success rates (with 95% confidence intervals [CI]) for stripping, foam sclerotherapy, radiofrequency ablation, and laser therapy were about 78% (70%-84%), 77% (69%-84%), 84% (75%-90%), and 94% (87%-98%), respectively. After adjusting for follow-up, foam therapy and radiofrequency ablation were as effective as surgical stripping (adjusted odds ratio [AOR], 0.12 [95% CI, –0.61 to 0.85] and 0.43 [95% CI, –0.19 to 1.04], respectively). Endovenous laser therapy was significantly more effective compared with stripping (AOR, 1.13; 95% CI, 0.40-1.87), foam therapy (AOR, 1.02; 95% CI, 0.28-1.75), and radiofrequency ablation (AOR, 0.71; 95% CI, 0.15-1.27).**
Conclusion: **In the absence of large, comparative randomized clinical trials, the minimally invasive techniques appear to be at least as effective as surgery in the treatment of lower extremity varicose veins. (J Vasc Surg 2009;49:230-9.)**

Lower-extremity venous insufficiency is a common medical condition and occurs in about 15% of men and 35% of women.[1-3] The effect of venous insufficiency on patients' health-related quality of life (HRQOL) is substantial and comparable with other common chronic diseases such as arthritis, diabetes, and cardiovascular disease.[4] In 1995 the overall cost associated with deep or superficial venous insufficiency, or both, was about 2.5% of the total health care budget in France and Belgium.[5]

The treatment of varicose veins alleviates symptoms and, hopefully, reduces the complication rate of venous insufficiency. The traditional gold standard in the treatment of varicosity of great saphenous veins (GSVs) is a high ligation at the saphenofemoral junction (SFJ), followed by stripping; conventional treatment of small saphenous veins (SSVs) is ligation at the saphenopopliteal junction (SPJ), often without stripping.

Surgery of varicose veins is usually performed under general or epidural anesthesia and may be associated with neurologic damage (about 7% in short and up to 40% in long stripping of GSVs),[6,7] scars, and postoperative pain. Despite the relatively high incidence, the neurologic damage has often little resultant morbidity. Although surgery is highly effective in the short term, the 5-year recurrence rates are approximately 30% for GSVs and 50% for SSVs, which may be due to neovascularization.[8,9] Only <10% of these recurrences are clinically relevant.

To improve effectiveness and patients' HRQOL and to reduce postoperative downtime, complications, and costs, new minimally invasive techniques such as ultrasound-guided foam sclerotherapy (UGFS),[10] radiofrequency ablation (RFA, VNUS Closure, VNUS Medical Technologies, San Jose, Calif),[11] and endovenous laser ablation (EVLA)[12] are now widely used in the treatment of lower extremity varicosities.

Although case series and comparative studies suggest lower recurrence rates of these minimally invasive interventions compared with surgical stripping, no large, long-term, comparative randomized controlled trials (RCTs)

From the Departments of Dermatology,[a] and Epidemiology and Biostatistics,[b] Erasmus MC, and Institute of Psychology, Erasmus University Rotterdam.[c]

Competition of interest: none.

Reprint requests: Tamar Nijsten, MD, PhD, Dermatology, Erasmus MC, Burg s'Jacobsplein 51, 3000 CA Rotterdam, The Netherlands (e-mail: t.nijsten@erasmusmc.nl).

0741-5214/$36.00

doi:10.1016/j.jvs.2008.06.030

have been performed yet, but some are ongoing.[13] The objective of this analysis is to systematically review and summarize the available studies on the surgical and new therapies and compare the effectiveness of these different options in order to assist physicians and patients in selecting the most appropriate intervention for lower extremity varicose veins in the current absence of well-designed RCTs.

METHODS

Because of the heterogeneity of the included studies, both the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) and Quality Of Reporting Of Meta-analyses (QUORUM) guidelines were used.[14,15]

Literature search. We initiated an electronic search of Medline, Cochrane Library, and Cinahl up to February 2007. PubMed was searched by a clinical librarian using the following algorithm: (sclerocompression *or* sclerotherapy) *or* ([{thermal *or* radiofrequency} *and* {ablation *or* obliteration}] *or* VNUS) *or* (laser *or* laser surgery) *or* (endovascular *or* endovenous) *or* (stripping *or* stripped *or* strip *or* strips *or* stripper *or* Babcock) *and* (saphenous *or* saphena *or* varicose veins *or* varicosis) *and* (duplex *or* Doppler *or* ultrasonic *or* ultrasound). To broaden the search, the "related articles" function was also used. Specialty journals such as *Dermatologic Surgery, Journal of Vascular Surgery, European Journal of Vascular and Endovascular Surgery,* and *Phlebology* were also searched electronically and references of identified studies and reviews were hand-searched. We reviewed all abstracts, studies, and citations, irrespective of language. Clinical trial registries were also searched.

Inclusion criteria. Our meta-analysis included RCTs, clinical trials, and prospective and retrospective case series on the treatment of human lower extremity varicosities by surgical stripping (SFJ ligation and GSV stripping or SPJ ligation [and SSV stripping]), EVLA (all wavelengths and energy parameters were included), UGFS with foam (multiple treatments were allowed and no distinction was made between type or concentration of sclerosant), and RFA. We were unable to differentiate between GSVs and SSVs because most studies that included both did not differentiate the outcomes. Only studies that used US examination as the outcome measure were eligible because US is considered the gold standard in the assessment of venous insufficiency and it increases the homogeneity of the analysis. For comparative studies, the arms of interest were included separately. All follow-up periods were allowed. English, German, French, and Dutch studies were included.

Exclusion criteria. Studies that performed SFJ ligation without stripping were excluded because this approach is considered suboptimal.[16] Studies that explicitly examined combination therapies were excluded. Treatments of nontruncal varicose veins were not included. We excluded UGFS studies that used liquid sclerosant because it is considered less effective than foam.[17] To our knowledge, there are no comparative RCTs suggesting a type of sclerosant is superior in the treatment of saphenous trunks using UGFS. Moreover, a RCT showed no significant difference between polidocanol and sodium tetradecyl sulfate in the treatment of varicose and telangiectatic veins, suggesting that the effect of the specific sclerosant in our analysis is limited.[18] If multiple articles reported the same study population, the publication with the longest follow-up was included.

Data extraction. The data of all eligible studies were analyzed by two authors (R. v. d. B. and T. N.) independently. The number of patients and treated limbs, the type of veins (GSV or SSV), the treatment procedure, the study type (retrospective or prospective), the duration of follow-up, the type of follow-up (mean follow-up, exact follow-up, or exact with loss of follow-up), the US outcome definitions, and success rate (if possible for GSVs and SSVs separately) were recorded. Because 89% of the included studies were case series, an extensive quality assessment of the studies was not performed, except that a distinction was made between retrospective and prospective data collection. Case series and the arms of interest of RCTs were entered separately in the analysis.

Standardization of outcome measures. All of the eligible studies used US as an outcome, but the definitions of treatment success by US examination varied considerably. Because the technical end point of each of the treatments is obliteration or complete removal (ie, anatomic success) of the insufficient vein, the definitions that closely reflected this objective were grouped by consensus of three authors (R. v. d. B., M. N., and T. N.). Therefore, US-based outcomes that used definitions such as absence of "detectable flow," "recurrence of reflux," "recanalization," "vein reopening," "recurrent or new varices," "closed vein," "occlusion," "obliteration," and "completely stripped vein" were considered to be equally successful. Studies that reported "clinical improvement," "patient satisfaction," "reflux at any site," "varicose veins present anywhere," and others were excluded.

Statistical analysis. After deriving the natural logarithm of the odds of success for all studies, we calculated pooled estimates of success rate and the 95% confidence interval (CI) for all four treatments using SAS PROC MIXED software (SAS Institute Inc, Cary, NC). A random-effect model[19-21] was used because a likelihood ratio test showed that the random-effect model fitted the data significantly better than did a fixed-effect model ($\chi^2_4 = 32.7$, $P < .001$).

We compared a random-effect model with one general random intercept to a multivariate random-effect model in which each treatment has its own random intercept. Because the latter did not improve the model significantly ($\chi^2_3 = 3.8$, $P = .28$), we used the random-effect model with one general random intercept only for all treatments. The treatments were used as covariates in the model, and the differences between the estimated log odds of the treatments automatically resulted in the log odds ratios (OR) to compare the treatments with each other.

Because follow-up time varied considerably within and between the four treatment groups and the decline of success percentages over time may differ per treatment, a

Table I. Characteristics of studies included in meta-analysis

No.	First author	Year[a]	Country	Study type[b]	No. of included limbs: Total	GSV	SSV	Therapy	Follow-up[c]	Success rate: Total	GSV	SSV	Definition of failure
1	Allegra	2007	Italy	1	1326	862	132	Surgery	60	0.75	0.87	0.7	Recurrent/new varices
2	Bountouroglu	2006	UK	3	30	30	0	Surgery	3	0.78	0.78	NA	Closed/occlusion/ obliteration
3	De Maseneer	2002	Belgium	1	172	172	0	Surgery	12	0.75	0.75	NA	Recurrent/new varices
4	De Medeiros	2005	Brazil	3	20	20	0	Surgery	1	1.00	1.00	NA	Re-opening
5	Dwerryhouse	1999	UK	1	52	52	0	Surgery	60	0.5	0.5	NA	Recurrent/new varices
6	Fischer	2001	Swiss	2	125	125	0	Surgery	408	0.4	0.4	NA	Recurrent/new varices
7	Frings	2004	Germany	1	500	500	0	Surgery	3	0.95	0.95	NA	Detectable flow/ reflux
8	Hartmann	2006	Germany	2	245	220	25	Surgery	168	0.69	0.66	0.88	Recurrent/new varices
9	Hinchliffe	2006	UK	3	16	16	0	Surgery	1.5	0.88	0.88	NA	Incomplete strip
10	Lurie	2005	USA	3	36	36	0	Surgery	24	0.79	0.79	NA	Recurrent/new varices
11	Perala	2005	Finland	3	13	13	0	Surgery	36	0.77	0.77	NA	Recurrent/new varices
12	Sarin	1994	UK	2	43	43	0	Surgery	21	0.51	0.51	NA	Detectable flow/ reflux
13	Smith	2002	UK	1	226	189	37	Surgery	12	0.86	0.91	0.62	Detectable flow/ reflux
14	Barrett 1[a]	2004	NZ	2	99	79	20	UGFS	23.7	0.69	...[d]	...[d]	Closed/occlusion/ obliteration
15	Barrett 1[b]	2004	NZ	2	17	14	3	UGFS	24.5	0.77	...[d]	...[d]	Closed/occlusion/ obliteration
16	Barrett 2	2004	NZ	2	100	98	23	UGFS	22.5	0.77	...[d]	...[d]	Closed/occlusion/ obliteration
17	Belcaro 1[e]	2000	Italy	3	39	39	0	UGFS	120	0.81	0.81	NA	Detectable flow/ reflux
18	Belcaro 2[e]	2003	Italy	3	211	211	0	UGFS	120	0.49	0.49	NA	Recurrent/new varices
20	Darke	2006	UK	1	143	115	28	UGFS	1.5	0.88	0.86	0.96	Closed/occlusion/ obliteration
21	Hamel-Desnos	2003	France	1	45	45	0	UGFS	0.75	0.84	0.84	...[d]	Detectable flow/ reflux
19	Smith	2006	UK	1	1411	886	263	UGFS	11	0.86	0.88	0.82	Closed/occlusion/ obliteration
22	Tessari	2001	Italy	1	24	9	7	UGFS	1	1	1	1	Closed/occlusion/ obliteration
23	Yamaki	2004	Japan	1	37	37	0	UGFS	12	0.68	0.68	NA	Closed/occlusion/ obliteration
24	Agus	2006	Italy	1	1068	1052	16	EVLA	36	0.97	...[d]	...[d]	Closed/occlusion/ obliteration
25	De Medeiros	2005	Brazil	1	20	20	0	EVLA	2	0.95	0.95	NA	Closed/occlusion/ obliteration
26	Disselhoff	2005	Netherlands	1	93	93	0	EVLA	3	0.84	0.84	NA	Closed/occlusion/ obliteration
27	Gerard	2002	France	1	20	20	0	EVLA	1	0.9	0.9	NA	Closed/occlusion/ obliteration
28	Gibson	2007	USA	1	210	156	210	EVLA	4	0.96	NA	0.96	Recanalization
29	Goldman	2004	USA	1	24	24	0	EVLA	8	1	1	NA	Detectable flow/ reflux
30	Huang	2005	China	1	19	19	0	EVLA	0.5	1	1	NA	Closed/occlusion/ obliteration
31	Kabnick	2006	USA	1	60	60	0	EVLA	12	0.93	0.93	NA	Detectable flow/ reflux
32	Kavuturu	2006	USA	1	66	66	0	EVLA	12	0.97	0.97	NA	Closed/occlusion/ obliteration
33	Kim 1	2006	USA	1	34	34	0	EVLA	12.2	1	1	NA	Recanalization

Table I. Continued

No.	First author	Year[a]	Country	Study type[b]	No. of included limbs Total	GSV	SSV	Therapy	Follow-up[c]	Success rate Total	GSV	SSV	Definition of failure
34	Kim 2	2006	USA	1	60	60	0	EVLA	6.8	0.97	0.97	NA	Closed/occlusion/obliteration
35	Marston	2006	USA	2	31	31	0	EVLA	0	0.84	0.84	NA	Closed/occlusion/obliteration
36	Morrison	2005	USA	1	50	50	0	EVLA	12	0.66	0.66	NA	Closed/occlusion/obliteration
37	Min 1	2001	USA	1	90	90	0	EVLA	9	0.96	0.96	NA	Closed/occlusion/obliteration
38	Min 2	2003	USA	1	499	499	0	EVLA	24	0.93	0.93	NA	Closed/occlusion/obliteration
39	Navarro	2001	USA	1	40	40	0	EVLA	4.2	1	1	NA	Detectable flow/reflux
40	Oh	2003	Korea	1	15	15	0	EVLA	3	1	1	NA	Closed/occlusion/obliteration
41	Perkowski	2004	USA	1	191	154	37	EVLA	0.5	0.97	. . .[d]	. . .[d]	Recanalization
42	Petronelli	2006	Italy	1	52	52	0	EVLA	12	0.93	0.93	NA	Recanalization
43	Proebstle 1	2002	Germany	1	31	31	0	EVLA	1	0.97	0.97	NA	Closed/occlusion/obliteration
44	Proebstle 2	2003	Germany	1	41	41	0	EVLA	6	0.95	0.95	NA	Recanalization
45	Proebstle 3	2004	Germany	2	106	106	0	EVLA	3	0.9	0.9	NA	Closed/occlusion/obliteration
46	Proebstle 4	2005	Germany	1	282	282	0	EVLA	3	0.98	0.98	NA	Closed/occlusion/obliteration
47	Proebstle 5	2006	Germany	1	263	263	0	EVLA	12	0.96	0.96	NA	Closed/occlusion/obliteration
48	Puggioni	2005	USA	2	77	77	0	EVLA	0.25	0.94	0.94	NA	Recanalization
49	Ravi	2006	USA	1	1091	990	101	EVLA	0.5	0.96	0.97	0.91	Recanalization
50	Sadick	2004	USA	1	30	30	0	EVLA	24	0.97	0.97	NA	Closed/occlusion/obliteration
51	Sharif	2006	UK	1	145	145	0	EVLA	12	0.76	0.76	NA	Closed/occlusion/obliteration
52	Theivacumar	2007	UK	1	68	0	68	EVLA	6	0.88	. . .	0.88	Closed/occlusion/obliteration
53	Timperman	2005	USA	1	100	83	0	EVLA	9	0.96	0.96	NA	Detectable flow/reflux
54	Dunn	2006	USA	1	85	85	0	RFA	6	0.9	0.9	NA	Closed/occlusion/obliteration
55	Fassiadis	2003	UK	1	59	59	0	RFA	3	1	1	NA	Closed/occlusion/obliteration
56	Goldman	2000	USA	1	12	12	0	RFA	6	1	1	NA	Closed/occlusion/obliteration
57	Goldman	2002	USA	1	41	41	0	RFA	13	0.68	0.68	NA	Closed/occlusion/obliteration
58	Hinchliffe	2006	UK	3	16	16	0	RFA	1.5	0.81	0.81	NA	Closed/occlusion/obliteration
59	Hingorani	2004	USA	1	73	73	0	RFA	0.3	0.96	0.96	NA	Closed/occlusion/obliteration
60	Lurie	2005	USA	1	46	46	0	RFA	24	0.86	0.86	NA	Recurrent/new varices
61	Marston	2006	USA	2	58	58	0	RFA	0	0.88	0.88	NA	Closed/occlusion/obliteration
62	Merchant 1	2002	USA	1	318			RFA	24	0.85	. . .[d]	. . .[d]	Closed/occlusion/obliteration
63	Merchant 2	2005	USA	1	1222	1154	52	RFA	60	0.87	. . .[d]	. . .[d]	Closed/occlusion/obliteration
64	Morrison	2005	USA	1	50	50	0	RFA	12	0.8	0.8	NA	Closed/occlusion/obliteration
65	Ogawa	2005	Japan	1	25	25	0	RFA	1	1	1	NA	Closed/occlusion/obliteration
66	Perala	2005	Finland	3	15	15	0	RFA	36	0.67	0.67	NA	Recurrent/new varices
67	Pichot	2004	France	2	63	63	0	RFA	25	0.91	0.91	NA	Closed/occlusion/obliteration

Table I. Continued

No.	First author	Year[a]	Country	Study type[b]	No. of included limbs: Total	GSV	SSV	Therapy	Follow-up[c]	Success rate: Total	GSV	SSV	Definition of failure
68	Puggioni	2005	USA	2	53	53	0	RFA	0.23	0.91	0.91	NA	Recanalisation
69	Sybrandy	2002	Netherlands	1	26	26	0	RFA	12	0.89	0.89	NA	Closed/occlusion/obliteration
70	Wagner	2003	USA	2	28	28	0	RFA	3	1	1	NA	Closed/occlusion/obliteration
71	Weiss	2002	USA	1	140	140	0	RFA	0	0.9	0.9	NA	Closed/occlusion/obliteration
72	Welch	2006	USA	2	184	184	0	RFA	0	0.8	0.8	NA	Closed/occlusion/obliteration

EVLA, endovenous laser ablation; *GSV,* great saphenous vein; *NA,* nonapplicable; *NZ,* New Zealand; *RCT,* randomized clinical trial; RFA, radiofrequency ablation; *SSV,* short saphenous vein; *UGFS,* ultrasound-guided foam sclerotherapy; *UK,* United Kingdom; *USA,* United States of America.
[a]Year of publication.
[b]Type 1 is prospective case series, type 2 is retrospective case series, and type 3 is a randomized clinical trial.
[c]Follow-up in months.
[d]Not documented separately for GSV and SSV.
[e]The surgery arm of this study was not included because only ligation without stripping was performed.

meta-regression with follow-up time per treatment as a covariate was performed to present success rates for different time intervals (ie, 3 months, 1, 3, and 5 years). Furthermore, we performed subgroup analysis based on the type of study (prospective vs retrospective) and study size (more or less than 60 limbs). The between-study variances of the models with and without these covariates were compared to assess whether heterogeneity in the covariates can explain part of the between-study variances.

RESULTS

Literature search. Of all screened abstracts and titles, 119 reports were reviewed in detail, and 64 studies (with a total of 72 arms) fulfilled the eligibility criteria. Of these, 13 (18%) reported on stripping, 10 (14%) on UGFS, 30 (42%) on EVLA, and 19 (26%) on RFA (Table I). We excluded 55 studies for several reasons (Fig 1).

Study characteristics for included trials. We included 64 studies (72 study arms) with a total of 12,320 treated limbs, of which 2804 (23%) were stripped, 2126 (17%) were treated by UGFS, 4876 (40%) by EVLA, and 2514 (20%) by RFA. The reports were published between January 1994 and February 2007, and 92% in the last 5 years (Table I). Of the 72 study arms, 58 (81%) were prospective. Although follow-up duration ranged from 1 day to 34 years, 51 of the 72 studies had a follow-up of between 3 months and 10 years. The number of included limbs was 12 to 1411. Nine studies reported the separate success rates of SSV and GSV therapy, and seven were RCTs that included two intervention arms. Nine of the 10 UGFS studies used aethoxysclerol (polidocanol), one study only used sodium tetradecyl sulfate, and three studies used both sclerosants.

Success rates for each therapy. The crude success rates of each of the four therapies independent of follow-up time according to the random-intercept model suggest that the success rate of EVLA (93.3%; 95% CI, 91.0-95.0) and

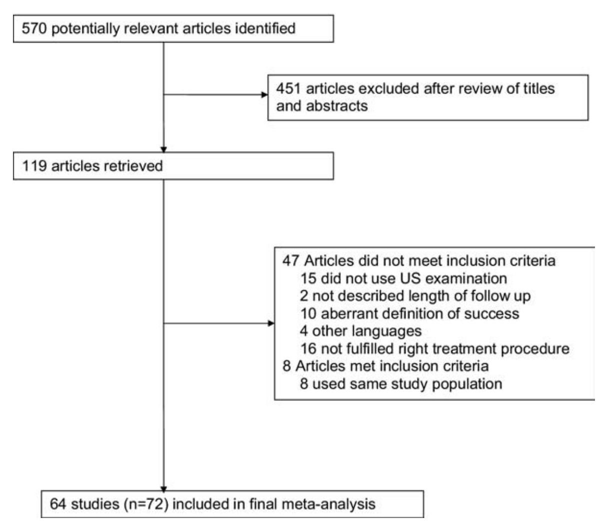

Fig 1. Schematic flow chart of literature search.

RFA (87.5%; 95% CI, 82.5-91.3) are higher than for stripping and UGFS (Fig 2). For stripping, UGFS, and RFA, the effectiveness of the therapies decreased over time from ≥80% success rates at 3 months to <80% after 5 years. The success percentages of EVLA remained at ≥92.9% (Table II, Fig 3). The estimated success rates declined significantly for stripping ($P = .004$), but no significant negative trend was detected for UGFS ($P = .08$), RFA ($P = .25$), or EVLA ($P = .61$) over time.

Comparison of therapies. Compared with stripping, UGFS was as effective and EVLA and RFA were significantly more effective in the treatment of lower extremity varicose veins (Table III). After adjusting for duration of follow-up, however, we observed no significant differences between stripping and RFA. Of the three minimally invasive techniques, EVLA was superior to UGFS ($P = .013$)

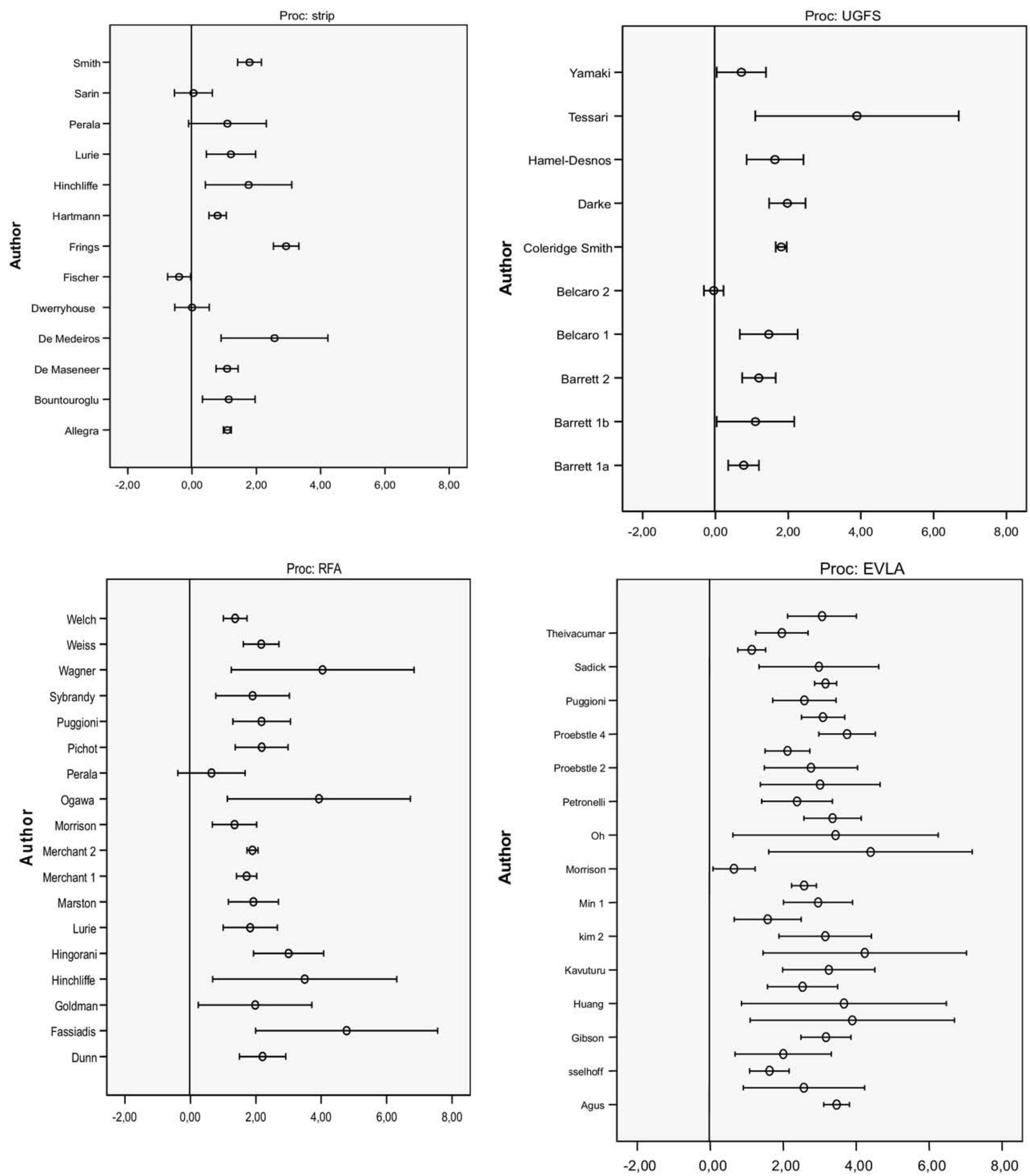

Fig 2. Forest plots with log(odds) of each study ordered per treatment.

and RFA ($P = .016$) after adjusting for follow-up time, but there was no significant difference between UGFS and RFA ($P = .27$).

Subgroup analysis. Restricting the analysis to the 58 prospective studies confirmed that EVLA was significantly more effective than stripping ($P < .0001$), UGFS ($P < .0001$), and RFA ($P = .01$). However, no significant differences in effectiveness were observed between RFA vs stripping ($P = .14$) and RFA vs UGFS ($P = .13$).

The results of the analyses of the 35 largest studies that treated >60 limbs were comparable with the complete meta-analysis: EVLA remained significantly more success-

Table II. The pooled proportion of patients with anatomical successful outcome after different time intervals

	3 months		*1 year*		*3 year*		*5 year*	
Type of intervention	*Success rate (%)*	*95% CI*	*Success rate (%)*	*95% CI*	*Success rate (%)*	*95% CI*	*Success rate (%)*	*95% CI*
Surgery	80.4	72.3-86.5	79.7	71.8-85.8	77.8	70.0-84.0	75.7	67.9-82.1
UGFS	82.1	72.5-88.9	80.9	71.8-87.6	77.4	68.7-84.3	73.5	62.8-82.1
RFA	88.8	83.6-92.5	87.7	83.1-91.2	84.2	75.2-90.4	79.9	59.5-91.5
EVLA	92.9	90.2-94.8	93.3	91.1-95.0	94.5	87.2-97.7	95.4	79.7-99.1

CI, Confidence intervals; *EVLA,* endovenous laser ablation; *RFA,* radiofrequency ablation; *UGFS,* ultrasound guided foam sclerotherapy.

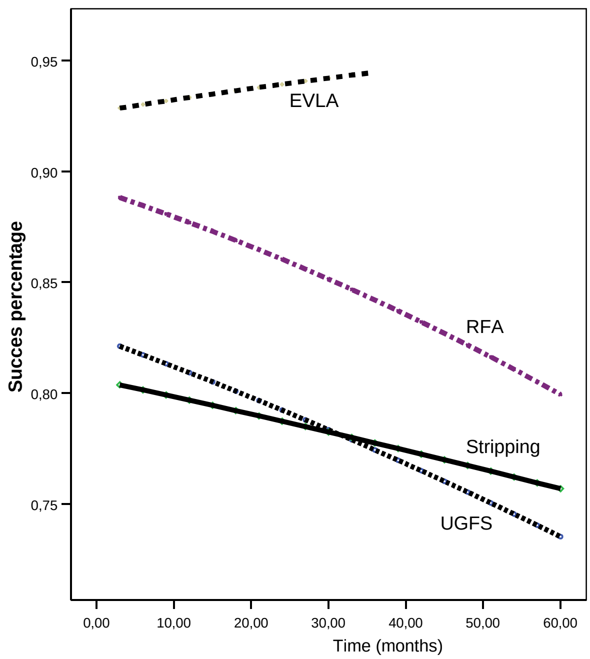

Fig 3. Anatomic success rate for surgical stripping, ultrasound-guided foam sclerotherapy *(UGFS),* endovenous laser ablation *(EVLA),* and radiofrequency ablation *(RFA)* in time. The estimated success rates declined significant for stripping ($P = .004$), but no significant negative trend was detected for UGFS ($P = .08$), RFA ($P = .25$), and EVLA ($P = .61$) over time.

ful than stripping ($P < .0001$), UGFS ($P < .0001$), and RFA ($P = .04$); and RFA was superior to stripping ($P = .048$) and UGFS ($P = .04$). Excluding the SSV and restricting the analysis to 62 studies that presented success rates for GSVs (separately) confirmed the finding that EVLA was significantly more effective than the other therapies ($P < .0001$).

DISCUSSION

The results of this meta-analysis suggest that endovenous treatments of lower extremity varicosities are better in achieving anatomic success (ie, obliteration or disappearance of veins) than surgery and UGFS. Of the endovenous therapies, EVLA is significantly more effective than RFA to obliterate the insufficient veins. These findings, however, should be confirmed in large, long-term, comparative RCTs.

The estimated success rates of the studied therapies and the comparison between therapies are in agreement with most of the available studies. A small paired analysis[22] and a nonrandomized pilot study that compared EVLA with stripping of the GSV[23] showed that the clinical efficacy parameters were comparable in the short term. A recent RCT showed that EVLA was as effective as stripping after 6 months and was associated with less postoperative pain and bruising.[24] In the long term, however, it is likely that the recurrence rate of surgery is higher than that of EVLA because of neovascularization, as is confirmed by the findings of the current analysis. One retrospective study suggested that RFA and EVLA were equally effective[25] and another that EVLA was superior.[26] Three small, short-term RCTs showed that RFA and surgery were about equally effective, but RFA-treated patients reported less postoperative pain and physical limitations, faster recovery, fewer adverse events, and superior HRQOL compared with patients who underwent surgical stripping.[27-29] An earlier RCT showed that liquid UGS was less effective than surgical stripping,[30] but that study used liquid sclerosant, which is washed out relatively quickly and induces less vasospasm and sclerous formation than foam sclerosant.[17] Clinical trial registries indicate that several important RCTs of RFA vs stripping and UGFS vs surgery are currently ongoing.[13]

In addition to anatomic success rates, patient-reported outcomes such as HRQOL, treatment satisfaction, symptom relief, and side effects are pivotal in a comparison between invasive and noninvasive therapies for venous insufficiency. Compared with surgery, EVLA-treated patients appreciated EVLA more than surgery because they reported fewer side effects and their HRQOL improved better and faster.[22,23] Patient-reported outcomes are especially important when two therapies are equally effective. For example, this current meta-analysis suggests that the anatomic success rates of UGFS and surgery are comparable, but patients' opinions may differ between these therapies.

Also, cost-effectiveness assessments are lacking and should be included in clinical trials. One study suggested that the RFA procedure was cost-saving from a societal perspective compared with surgery because the patient's physical function was restored faster and endovenous ther-

Table III. Comparisons of four different treatment options for lower extremity varicose veins

	Unadjusted for follow-up			*Adjusted for follow-up*		
Comparisons	*Crude OR*	*95% CI*	*P*	*Adjusted OR*	*95% CI*	*P*
UGFS vs strip	0.15	–0.49 to 0.80	.64	0.12	–0.61 to 0.85	.73
EVLA vs strip	1.54	1.02 to 2.07	<.0001	1.13	0.40 to 1.87	.006
RFA vs strip	0.87	0.29 to 1.45	.003	0.43	–0.19 to 1.04	.16
EVLA vs UGFS	1.39	0.81 to 1.97	<.0001	1.02	0.28 to 1.75	.013
RFA vs UGFS	0.71	0.08 to 1.34	.03	0.31	–0.29 to 0.91	.27
EVLA vs RFA	0.68	0.17 to 1.18	.009	0.71	0.15 to 1.27	.016

CI, Confidence intervals; *EVLA,* endovenous laser ablation; *OR*, odds ratio; *RFA,* radiofrequency ablation; *UGFS,* ultrasound guided foam sclerotherapy.

apies can be performed in an outpatient setting, resulting in lower nonmedical costs.[27]

Minor and relatively common postoperative complications of ligation and stripping are wound infection, hematoma, lymphorrhagia, and hypertrophic scarring. Other complications of surgery are nerve injury (7%) and deep vein thrombosis (<2%).[31-36] Because the sclerosant enters the deep venous system, UGFS may be associated with several specific complications such as migraine, temporal brain ischaemia, and scotomas, especially among patients with a foramen ovale.[37] As in surgery, most patients will experience ecchymosis and pain (often described as "a pulling chord") for 1 to 2 weeks after endovenous therapies. Dysesthesia, phlebitis, and skin burns have been reported in a small proportion and deep vein thrombosis in <1% of patients after EVLA and RFA.[38-41]

To our knowledge, this is the first meta-analysis and meta-regression analysis comparing different treatment options for lower extremity varicose veins, and the results suggest that there are significant differences between interventions. The detected differences are in accordance with the few available comparative studies suggesting a good face validity of our findings. More than 60 studies met our inclusion criteria. To increase homogeneity of the comparison, we restricted the analysis to studies that used US as primary end point. Because of the variation in follow-up duration, we adjusted the comparison between the therapies for this difference. Several sensitivity analyses were performed to assess the effects of study design, duration of follow-up, and sample size on our findings and they confirmed our initial results.

Meta-analysis is associated with several limitations. A major limitation of this analysis is that it included a heterogeneous mix of case series and RCTs. This rather unusual but methodologically and clinically sound approach was chosen because of the lack of comparative RCTs in phlebology, as was illustrated by the systematic review. To increase the quality of analysis, both the MOOSE and QUORUM guidelines were followed as much as possible.[14,15] The objective of this study was to inform physicians about four therapies commonly used in the treatment of lower extremity varicose veins and compare their efficacy based on the available data.

An aggregation or ecologic bias, which occurs because group rates may not resemble individual rates, is unavoidable. Because we were unable to precisely describe the heterogeneous study populations, different inclusion criteria may have affected our findings (eg, case series of endovenous therapies may have included more primary, nontortuous, interfascial GSVs than UGFS and stripping, and RFA is limited to veins of ≤12 mm due to the catheter size). Although we restricted the analysis to studies that used US to increase comparability, the standardization of the different definitions of success, which was based on consensus, may have affected our results.

To minimize the effect of publication bias, an extensive English and non-English literature search was performed, including registries of clinical trials. Small studies were not excluded to reduce publication bias because their impact was weighted and the proportion of total weight of these studies was limited. A subanalysis limited to studies with >60 patients showed findings similar to those presented, confirming that the effect of the smaller studies was not substantial.

The EVLA studies with limited follow-up are likely to reflect the centers' initial experience (ie, learning curve), and the relatively large proportion of these studies may explain the lower success rates after 3 months compared with later intervals. Several studies from the 1970s and 1980s were excluded because US examination was not an outcome measurement. To further increase homogeneity of the analysis, it was restricted to studies that used ligation and stripping because this is the gold standard of surgical care and restricted to foam in sclerotherapy because it is superior to liquid sclerosant.[17] Also, we did not differentiate between concentration of sclerosant, which varied from 1% to 3%. However, a recent RCT demonstrated that the concentration of sclerosant (1% vs 3%) was not a significant predictor of outcome in UGFS.[42] Because 89% of the studies were case series, a thorough quality assessment was not performed, but subgroup analysis suggests that the results of retrospective and prospective studies were not substantially different.

CONCLUSION

The results of this meta-analysis support the increasing use of minimally invasive interventions in the treatment of lower extremity varicosities. In the absence of comparative RCTs, it appears that EVLA is more effective than surgery, UGFS, and RFA. However, large, long-term comparative RCTs that include patient-reported outcomes, cost-effectiveness analyses, and safety assessment are needed to achieve the highest level of evidence for these novel therapies.

AUTHOR CONTRIBUTIONS

Conception and design: TN, LA, MN
Analysis and interpretation: TN, LA
Data collection: RB, TN, MK
Writing the article: RB, TN, LA
Critical revision of the article: MK, MN, LA
Final approval of the article: RB, MK, MN, LA, TN
Statistical analysis: LA
Obtained funding: Not applicable
Overall responsibility: TN

REFERENCES

1. Callam MJ. Epidemiology of varicose veins. Br J Surg 1994;81:167-73.
2. Evans CJ, Fowkes FGR, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Community Health 1999;53:149-53.
3. Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. J Am Acad Dermatol 2002;46:381-6.
4. Andreozzi GM, Cordova RM, Scomparin A, Martini R, D'Eri A, Andreozzi F; Quality of Life Working Group on Vascular Medicine of SIAPAV. Quality of life in chronic venous insufficiency. An Italian pilot study of the Triveneto Region. Int Angiol 2005;24:272-7.
5. Van den Oever R, Hepp B, Debbaut B, Simon I, Socio-economic impact of chronic venous insufficiency. An underestimated public health problem. Int Angiol 1998;17:161-7.
6. Morrison C, Dalsing MC. Signs and symptoms of saphenous nerve injury after greater saphenous vein stripping: prevalence, severity, and relevance for modern practice. J Vasc Surg 2003;38:886-90.
7. Holmes JB, Skajaa K, Holme K. Incidence of lesions of the saphenous nerve after partial or complete stripping of the long saphenous vein. Acta Chir Scand 1990;156:145-8.
8. Hartmann K, Klode J, Pfister R, Toussaint M, Weingart I, Waldermann F, et al. Recurrent varicose veins: sonography-based re-examination of 210 patients 14 years after ligation and saphenous vein stripping. Vasa 2006;35:21-6.
9. Darke SG. The morphology of recurrent varicose veins. Eur J Vasc Surg 1992;6:512-7.
10. Belcaro G, Nicolaides AN, Ricci A, Dugall M, Errichi BM, Vasdekis S, et al. Endovascular sclerotherapy, surgery, and surgery plus sclerotherapy in superficial venous incompetence: a randomized, 10-year follow-up trial–final results. Angiology 2000;51:529-34.
11. Goldman MP. Closure of the greater saphenous vein with endoluminal radiofrequency thermal heating of the vein wall in combination with ambulatory phlebectomy: preliminary 6-month follow-up. Dermatol Surg 2000;26:452-6.
12. Navarro L, Min RJ, Bone C. Endovenous laser: a new minimally invasive method of treatment for varicose veins–preliminary observations using an 810 nm diode laser. Dermatol Surg 2001;27:117-22.
13. Current controlled trials. www.controlled-trials.com. Current Controlled Trials Ltd.
14. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008-12.
15. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896-900.
16. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five-year results of a randomized trial. J Vasc Surg 1999;29:589-92.
17. Hamel-Desnos C, Desnos P, Wollmann JC, Ouvry P, Mako S, Allaert FA. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. Dermatol Surg 2003;29:1170-5.
18. Rao J, Wildemore JK, Goldman MP. Double-blind prospective comparative trial between foamed and liquid polidocanol and sodium tetradecyl sulfate in the treatment of varicose and telangiectatic leg veins. Dermatol Surg 2005;31:631-5.
19. Houwelingen HC van, Zwinderman KH, Stijnen T. Bivariate approach to meta-analysis. Stat Med 1993;12:2273-84.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
21. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002;21:589-624.
22. De Medeiros CA, Luccas GC. Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose veins. Dermatol Surg 2005;31:1685-94.
23. Mekako AI, Hatfield J, Bryce J, Lee D, McCollum PT, Chetter I. A nonrandomised controlled trial of endovenous laser therapy and surgery in the treatment of varicose veins. Ann Vasc Surg 2006;20:451-7.
24. Rasmussen LH, Bjoern L, Lawaetz M, Blemings A, Lawaetz B, Eklof B. Randomized trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: short-term results. J Vasc Surg 2007;46:308-15.
25. Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P. Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: analysis of early efficacy and complications. J Vasc Surg 2005;42:488-93.
26. Almeida JI, Raines JK. Radiofrequency ablation and laser ablation in the treatment of varicose veins. Ann Vasc Surg 2006;20547–52.
27. Rautio T, Ohinmaa A, Perala J, Ohtonen P, Heikkinen T, Wiik H, et al. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of the costs. J Vasc Surg 2002;35:958-65.
28. Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). J Vasc Surg 2003;38:207-14.
29. Perala J, Rautio T, Biancari F, Ohtonen P, Wiik H, Heikkinen T, et al. Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3-year outcome of a randomized study. Ann Vasc Surg 2005;19:669-72.
30. Rutgers PH, Kitslaar PJ. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. Am J Surg 1994;168:311-5.
31. Cox SJ, Wellwood JM, Martin A. Saphenous nerve injury caused by stripping of the long saphenous vein. BMJ 1974;1:415-7.
32. Docherty JG, Morrice JJ, Bell G. Saphenous neuritis following varicose vein surgery. Br J Surg 1994;81:698.
33. Morrison C, Dalsing MC. Signs and symptoms of saphenous nerve injury after greater saphenous vein stripping: prevalence, severity, and relevance for modern practice. J Vasc Surg 2003;38:886-90.
34. Sam RC, Silverman SH, Bradbury AW. Nerve injuries and varicose vein surgery. Eur J Vasc Endovasc Surg 2004;27:113-20.
35. Wood JJ, Chant H, Laugharne M, Chant T, Mitchell DC. A prospective study of cutaneous nerve injury following long saphenous vein surgery. Eur J Vasc Endovasc Surg 2005;30:654-8.
36. Holme JB, Skajaa K, Holme K. Incidence of lesions of the saphenous nerve after partial or complete stripping of the long saphenous vein. Acta Chir Scand 1990;156:145-8.
37. Smith PC. Chronic venous disease treated by ultrasound guided foam sclerotherapy. Eur J Vasc Endovasc Surg 2006;32:577-83.
38. Agus GB, Mancini S, Magi G; IEWG. The first 1000 cases of Italian Endovenous-laser Working Group (IEWG). Rationale, and long-term outcomes for the 1999-2003 period. Int Angiol 2006;25:209-15.

39. Proebstle TM, Moehler T, Gul D, Herdemann S. Endovenous treatment of the great saphenous vein using a 1,320 nm Nd:YAG laser causes fewer side effects than using a 940 nm diode laser. Dermatol Surg 2005;31:1678-83.
40. Kabnick LS. Outcome of different endovenous laser wavelengths for great saphenous vein ablation. J Vasc Surg 2006;43:88-93.
41. Merchant RF, Pichot O; Closure Study Group. Long-term outcomes of endovenous radiofrequency obliteration of saphenous reflux as a treatment for superficial venous insufficiency. J Vasc Surg 2005;42:502-9.
42. Ceulen RP, Bullens-Goessens YL, Pi-VAN DE Venne SJ, Nelemans PJ, Veraart JC, Sommer A. Outcomes and side effects of duplex-guided sclerotherapy in the treatment of great saphenous veins with 1% versus 3% polidocanol foam: results of a randomized controlled trial with 1-year follow-up. Dermatol Surg 2007;33:276-81.

Submitted Feb 13, 2008; accepted Jun 10, 2008.