A randomized controlled noninferiority trial comparing radiofrequency with stripping and conservative hemodynamic cure for venous insufficiency technique for insufficiency of the great saphenous vein

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CME Activity

Purpose or Statement of Need The purpose of this journal-based CME activity is to enhance the vascular specialist's ability to diagnose and care for patients with the entire spectrum of circulatory disease through a comprehensive review of contemporary vascular surgical and endovascular literature.

Learning Objective

- Describe the procedure and anticipated outcomes of three commonly used techniques to treat saphenous vein reflux in patients with chronic venous insufficiency

Target Audience This activity is designed for vascular surgeons and individuals in related specialties.

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ABSTRACT

Objective: The quality of available evidence regarding new minimally invasive techniques to abolish great saphenous vein reflux is moderate. The present study assessed whether radiofrequency ablation (RFA) was noninferior to high ligation and stripping (HLS) and conservative hemodynamic cure for venous insufficiency (CHIVA) for clinical and ultrasound recurrence at 2 years in patients with primary varicose veins (VVs) due to great saphenous vein (GSV) insufficiency.

Methods: We performed a randomized, single-center, open-label, controlled, noninferiority trial to compare RFA and 2 surgical techniques for the treatment of primary VVs due to GSV insufficiency. The noninferiority margin was set at 15% for absolute differences. Patients aged >18 years with primary VVs and GSV incompetence, with or without clinical symptoms, C2 to C6 CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) clinical class, and GSV diameter >4 mm were randomized with a 1:1:1 ratio to RFA, HLS, or CHIVA. The rate of clinical recurrence at 24 months was the primary endpoint and was analyzed using a delta noninferiority margin of 15%. Ultrasound recurrence, safety, and quality of life were secondary endpoints.

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Results: From December 2012 to June 2015, 225 limbs had been randomized to RFA, HLS, or CHIVA (n = 74, n = 75, and n = 76). Clinical follow-up and Doppler ultrasound examinations were performed at 1 week and 1, 6, 12, and 24 months postoperatively. No differences in postoperative complications or pain were observed among the three groups. RFA was noninferior to HLS and CHIVA for clinical recurrence at 24 months, with an estimated difference in recurrence of 3% (95% confidence interval [CI], −4.8% to 10.7%; noninferiority $P = .002$) and −7% (95% CI, −17% to 3%; $P < .001$), respectively. For ultrasound recurrence, RFA was noninferior to CHIVA, with an estimated difference of −34% (95% CI, −47% to −20%; noninferiority $P < .001$) at 24 months. However, noninferiority could not be demonstrated compared with HLS (5.9%; 95% CI, −4.1 to 15.9; $P = .073$). No differences were found in quality of life among the three groups.

Conclusions: RFA was shown to be noninferior in terms of clinical recurrence to HLS and CHIVA in the treatment of VVs due to GSV insufficiency. (J Vasc Surg: Venous and Lym Dis 2021;9:101-12.)

Keywords: Catheter ablation; CHIVA; Randomized controlled trial; Stripping; Varicose veins

Chronic venous disease (CVD) includes a set of clinical syndromes whose pathophysiology is venous hypertension.[1] The clinical presentation ranges from benign and asymptomatic varicose veins (VVs) to more severe scenarios such as hyperpigmentation and leg ulceration. Its effect on patient quality of life (QoL) can be substantial,[2] and different treatments can result in significant improvements.[3,4] Up to 60% to 70% of VVs result from great saphenous vein (GSV) incompetence.[5]

VVs have traditionally been treated with high ligation at the saphenofemoral junction (SFJ), followed by stripping to the knee[6] (high ligation and stripping [HLS]). However, recurrences after conventional surgery have been frequent (range, 13%-65% at 5 years).[7-9] Conservative hemodynamic cure for venous insufficiency (CHIVA) is an ultrasound-guided strategy widely used in some European countries.[10-13] The CHIVA method preserves, not only the GSV, but also the normal venous drainage of the superficial tissues of the limb. It has shown lower rates of clinical recurrence compared with conventional surgery.[14] However, no data are available regarding the efficacy of CHIVA compared with any of the newer minimally invasive endovenous techniques such as radiofrequency ablation (RFA).[15]

In the past 2 decades, endovenous thermal ablation treatments, such as RFA and endovenous laser, have been developed to abolish GSV reflux, with less postoperative pain, a shorter recovery time, and improvement in QoL.[16-18] Evidence has suggested that RFA is at least as effective as surgery for the treatment of VVs. Thus, additional studies to demonstrate the superiority of RFA compared with other techniques should be performed.[19] Our hypothesis was that RFA would be noninferior to HLS and CHIVA in clinical and Doppler ultrasound (DUS) success and could reduce surgical morbidity with better effects on QoL. Our aim was to compare the efficacy in terms of clinical and DUS recurrence at 2 years and assess the procedural safety, postoperative pain, and QoL of patients treated with RFA compared with HLS and CHIVA.

METHODS

Study design

A randomized, controlled, open-label, noninferiority trial comparing three surgical techniques to treat patients with primary VVs due to GSV incompetence was performed to test the noninferiority of RFA compared with HLS or CHIVA. The present single-center study was conducted in the vascular surgical department of a university hospital.

Inclusion and exclusion criteria

Consecutive adult patients aged >18 years who had presented with VVs and primary GSV incompetence (reflux >0.5/s), an outer GSV diameter >4 mm, and C2 to C6 in the CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) classification, with or without symptoms were invited to participate in the present study (Table I). All included patients provided written informed consent before any study procedure was performed. During the first visit, a DUS examination was performed, and the following information was collected: sociodemographic and pathologic data, CEAP classification, the presence of symptoms (pain, heaviness, itching, or cramps), and other parameters related to venous insufficiency. A baseline estimation of the QoL was obtained using validated disease-specific (chronic venous insufficiency quality of life questionnaire [CIVIQ]) and general (36-item short-form survey [SF-36]) questionnaires.[20] Patients with severe comorbidities (Table I) or previous surgery or sclerotherapy treatment of VVs in the same leg were excluded.

Randomization procedures

Randomization to 1 of the 3 techniques (ie, RFA, HLS, CHIVA) was performed using computer-generated random numbers and balanced using randomly permuted blocks of 9. Sequentially numbered, opaque, sealed envelopes were available for the consultant surgeon during the preoperative visit. The patients who had met the inclusion criteria and were considered eligible provided written consent, and the envelope was opened. The surgeons and patients were not kept

Table I. Inclusion and exclusion criteria

Criteria
Inclusion
Age ≥18 years
Primary varicose veins according to the CEAP classification (≥2)
Written informed consent to participate in study
Reflux of supragenicular GSV measured by DUS >0.5 seconds and diameter >4.0 mm
Exclusion
Active neoplasia or severe or debilitating systemic disease
Severe psychiatric diseases: psychotic disorders or major depression
Pregnancy
Recurrent varicose veins
Previous treatment with sclerosis agents
Previous or active deep venous thrombosis
Hematologic disorders
Anticoagulation treatment
Inclusion in any other clinical trial

CEAP, Clinical, Etiologic, Anatomic, Pathophysiologic; *DUS*, duplex ultrasound; *GSV*, great saphenous vein.

ARTICLE HIGHLIGHTS

- **Type of Research:** Prospective, single-center, randomized, noninferiority trial
- **Key Findings:** 225 limbs with primary varicose veins and great saphenous vein incompetence were randomized to treatment with radiofrequency ablation (RFA), high ligation and stripping (HLS), or conservative hemodynamic cure for venous insufficiency (CHIVA). No differences in postoperative complications or quality of life were observed. At 24 months, RFA was noninferior to HLS and CHIVA for clinical recurrence and to CHIVA for ultrasound recurrence. The clinical recurrence rate at 24 months was as follows: HLS, 4.3%; RFA, 7.2%; and CHIVA, 14.7%. The ultrasound recurrence rate was follows: HLS, 7.1%; RFA, 13%; and CHIVA, 46.7%.
- **Take Home Message:** RFA was noninferior to HLS and CHIVA in terms of clinical recurrence and quality of life at 24 months.

unaware of the surgical procedure, and the patients were informed of the surgical technique assigned just before surgery. Patients with bilateral VVs could be randomized twice, with a minimum period of 1 year between treatments. Vascular surgeons in charge of the clinical and DUS follow-up examinations were kept unaware of the surgical technique used.

Intervention description

Surgery was performed in the outpatient surgical unit, and all patients were discharged on the same day of the intervention. Most patients had received general or regional anesthesia, except for those patients who had undergone the CHIVA technique, for whom local anesthesia was predominant. DUS scanning was performed before the intervention to mark the GSV and VVs for phlebectomy.[21]

- Conventional surgery (HLS): complete disconnection of the SFJ and tributaries was performed using nonabsorbable sutures, with invaginating stripping of the above the knee GSV using a disposable stripper (Dormo-Strip, model no.VE-022; Hibernia Medical, Dublin, Ireland).
- RFA: a 7-cm heating intraluminal catheter (VNUS ClosureFast; Medtronic, Dublin, Ireland) was inserted percutaneously into the GSV, positioned 2 cm below the SFJ using ultrasound guidance. Tumescent local infiltration was performed with saline solution. Segmental energy at 120°C was delivered in 20-second cycles. Two cycles were applied in the proximal vein, followed by 1 or 2 cycles in the following segment. The remainder of the above the knee GSV was treated with 1 cycle.
- CHIVA: a DUS-guided strategy was used, according to the hemodynamics, with preservation of the GSV. A single surgical procedure was performed, consisting of fragmentation of the blood column by interruption of the refluxing saphenous trunks, disconnection of venous–venous shunts, and abolition of undrained VVs, with preservation of the communicating perforator veins (re-entry points).

Concomitant phlebectomy was performed in all 3 surgical procedures.

Postoperative management

All the patients received prophylactic low-molecular-weight heparin after surgery for 7 days. A nonstretch compression bandage was applied from the foot to the groin. After 48 hours, it was replaced by a compression stocking (23-32 mm Hg) for 4 weeks. Analgesic treatment with acetaminophen and ibuprofen was prescribed.

Patient follow-up

Clinical and DUS examinations were performed by an independent senior observer who was unaware of the surgical technique used at 1 week and 1, 6, 12, and 24 months postoperatively. The occurrence of serious adverse events (deep vein thrombosis [DVT]), pulmonary embolism [PE], death) and surgery-related complications, diagnosed by clinical and visual examination, such as bruising, hematoma (defined as any blood collection >3 × 3 cm in the surgical area with bulging of the tissues involved in the path of the supragenicular GSV or surgical phlebectomy), wound infection, hyperpigmentation, nerve injury (dysesthesia along the GSV or phlebectomy described by the patient as burning pain, pinching, or cramping), and superficial vein

Table II. Criteria for clinical and ultrasound recurrence ≥6 months postoperatively stratified by surgical procedure

Clinical recurrence
HLS
New and palpable VVs >4 mm, absent at 1-month follow-up that subsequently appeared owing to neovascularization or tactical or technical error
RFA
New and palpable VVs >4 mm, absent at 1-month follow-up that subsequently appeared owing to neovascularization or tactical or technical error
CHIVA
New and palpable VVs >4 mm, absent at 1-month follow-up that subsequently appeared owing to neovascularization or tactical or technical error
Ultrasound recurrence (≥1 criterion)
HLS
Patent segment of supragenicular GSV > 5 cm in length
Perforator incompetence, neovascularization from SFJ, pelvic collaterals, or VVs from anterior accessory saphenous vein in thigh
RFA
Patent segment of treated supragenicular GSV >5 cm long
Perforator incompetence, neovascularization from SFJ, pelvic collaterals, or VVs from anterior accessory saphenous vein in thigh
CHIVA
Insufficient GSV without leg perforator drainage causing new VVs
Perforator incompetence, neovascularization from SFJ, pelvic collaterals, or VVs from anterior accessory saphenous vein in thigh

CHIVA, Conservative hemodynamic cure for venous insufficiency; *GSV,* great saphenous vein; *HLS,* high ligation and stripping; *RFA,* radiofrequency ablation; *VVs,* varicose veins; *SFJ,* saphenofemoral junction.

thrombosis (inflammation and clotting in a superficial vein due to thrombosis diagnosed by clinical evaluation and DUS) were recorded during the follow-up visits. Pain severity was assessed using a visual analog scale (VAS) at 24 hours, 1 week, and 1 month postoperatively. The Venous Clinical Severity Score (VCSS) was calculated at 6 and 24 months postoperatively.

Study endpoints

Primary endpoint. The primary endpoint was clinical recurrence at 24 months, defined as the visual and palpable detection by an independent observer of new VVs that had been absent at the 1-month examination (Table II). The definition of VV recurrence was determined from the REVAS (recurrent varicose veins after surgery) classification[8]: "the existence of varicose veins in a lower limb previously operated on for varicosities, with or without adjuvant therapies, which includes true recurrences, residual veins and new varices, as a result of disease progression."

Secondary endpoints. DUS recurrence was included as a secondary endpoint. Because RFA, HLS, and CHIVA use different mechanisms to abolish reflux, each has a different definition of DUS recurrence (Table II). Ulcer recurrence and ulcer healing were also recorded for patients with advanced venous disease (CEAP class 6). The other secondary endpoints included short- and long-term complications, including bruising, above the knee hematoma, wound infection or bleeding, nerve injury, superficial vein thrombosis, scar induration, keloid scar or above the knee pigmentation, DVT, PE, and death. Mean postoperative pain was assessed using a VAS at 24 hours, 1 week, and 1 month postoperatively, and the VCSS was measured at 6 and 12 months postoperatively. Changes in QoL were evaluated from baseline using the CIVIQ-20 and SF-36 scores at different times postoperatively.

Statistical analysis

The main analysis was performed for the intention to treat (ITT) population, defined as all randomized patients who had undergone surgery. A secondary sensitivity analysis was conducted to calculate the rate of recurrence at 24 months in a modified ITT population, including all randomized patients who had undergone surgery with ≥1 follow-up DUS examination at ≥6 months postoperatively. The patients were analyzed in each assigned surgical technique group. Missing data imputation at the 24-month point was performed as follows. First, patients with recurrence at any time after the surgical procedure were considered to have had recurrence at 2 years. Second, patients without recurrence at 20 months postoperatively were considered to be recurrence free at 2 years. Finally, patients without a 24-month follow-up visit but with follow-up examinations from 24 to 28 months were assigned the outcome of that visit.

The hypothesis proposed was that the difference between the proportion of procedures with clinical and DUS recurrence in the RFA group minus those in the HLS and CHIVA groups would be lower than an absolute

Table III. Patient baseline characteristics

Characteristic	RFA (n = 69)	HLS (n = 70)	CHIVA (n = 75)
Age, years	47.9 (45.06-50.78)	49.44 (46.39-52.49)	47.55 (44.9-50.19)
BMI, kg/m^2	27 (26-28)	26.5 (25.7-27.3)	27.2 (26.2-28.2)
BMI group, kg/m^2			
<25	27 (39.1)	27 (38.5)	25 (33.3)
25-30	25 (36.2)	28 (40)	31 (41.3)
>30	17 (24.6)	15 (21.4)	19 (25.3)
Female gender	43 (62.3)	44 (62.9)	40 (53.3)
CEAP classification			
Symptomatic (yes)	58 (84.1)	62 (88.6)	59 (78.7)
C2, varicose veins	35 (50.7)	28 (40)	43 (57.3)
C3, edema	23 (33.3)	28 (40)	23 (30.7)
C4, pigmentation or eczema/lipodermatosclerosis	9 (13)	11 (15.7)	9 (12)
C5, healed venous ulcer	2 (2.9)	1 (1.4)	0 (0)
C6, active venous ulcer	0 (0)	2 (2.9)	0 (0)
GSV diameter before intervention, mm	6.86 (6.37-7.35)	7.18 (6.64-7.72)	6.52 (6.15-6.86)
Shunt type			
Type 2 (2B)	0 (0)	0 (0)	2 (2.7)
Type 1+2 or 2+1	1 (1.4)	6 (8.6)	6 (8)
Type 3	62 (89.9)	57 (81.4)	54 (72)
Type 4+2	2 (2.9)	1 (1.4)	1 (1.3)
Type 5	4 (5.8)	6 (8.6)	12 (16)
GIS (CIVIQ)	29.9 (24.5-35.3)	29.1 (24.3-33.8)	28.7 (24.2-33.3)
SF-36			
PCS	72.8 (67.7-77.9)	75.3 (70.5-80.1)	72.7 (67.1-78.3)
MCS	73.1 (68-78.1)	75.7 (70.5-80.9)	72.9 (67.4-78.4)

BMI, Body mass index; *CEAP*, Clinical, Etiologic, Anatomic, Pathophysiologic; *CHIVA*, conservative hemodynamic cure for venous insufficiency; *CIVIQ*, chronic venous insufficiency quality of life questionnaire; *GIS*, global index score; *GSV*, great saphenous vein; *HLS*, high ligation and stripping; *MCS*, mental component score; *PCS*, physical component score; *RFA*, radiofrequency ablation; *SF-36*, 36-item short-form survey.
Data are presented as mean (95% confidence interval) or number (%).

15% delta. The noninferiority of RFA compared with HLS and CHIVA would be declared if the upper limit of the 95% confidence interval (CI) for the difference in the proportions was less than the margin of noninferiority, calculated using the Newcombe-Wilson method. *P* values for noninferiority were also calculated. Because two comparisons were established as co-primaries (RFA with HLS and RFA with CHIVA) and because this statistical approach implies that both results must be confirmed to achieve the main objective, no multiplicity adjustments were performed. A Kaplan-Meier analysis for clinical and DUS recurrence was performed, comparing the groups using a log-rank test, for the overall and pairwise comparisons. Relative differences in risk between RFA and HLS and RFA and CHIVA were also estimated using hazard ratios (HRs), with the 95% CI, from Cox proportional hazard regression models. Assumptions of the Cox models were verified by plotting the log of the negative log of the survival function against the log of time. These analyses were performed to assess the robustness of the predefined main statistical analyses and differences in the rates described in the protocol.

The patients' clinical course, QoL (CIVIQ, SF-36), VCSS, and pain (VAS) were evaluated using generalized estimating equations models, with an autoregressive order correlation matrix to account for intraindividual correlations, considering the surgical procedure and group by time interaction as factors. All statistical analyses were performed using SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY), with a two-sided type I error of 0.05.

Sample size

The sample size was calculated using the primary endpoint. Assuming a common rate of clinical recurrence of 10% at 2 years for all treatment groups and a noninferiority margin of 15% for absolute differences, with a single-sided alpha risk of 2.5%, 65 to 70 patients per group would be required. The trial had 78% to 82% power to assess this noninferiority. To account for patient withdrawal, 225 patients were eventually recruited.

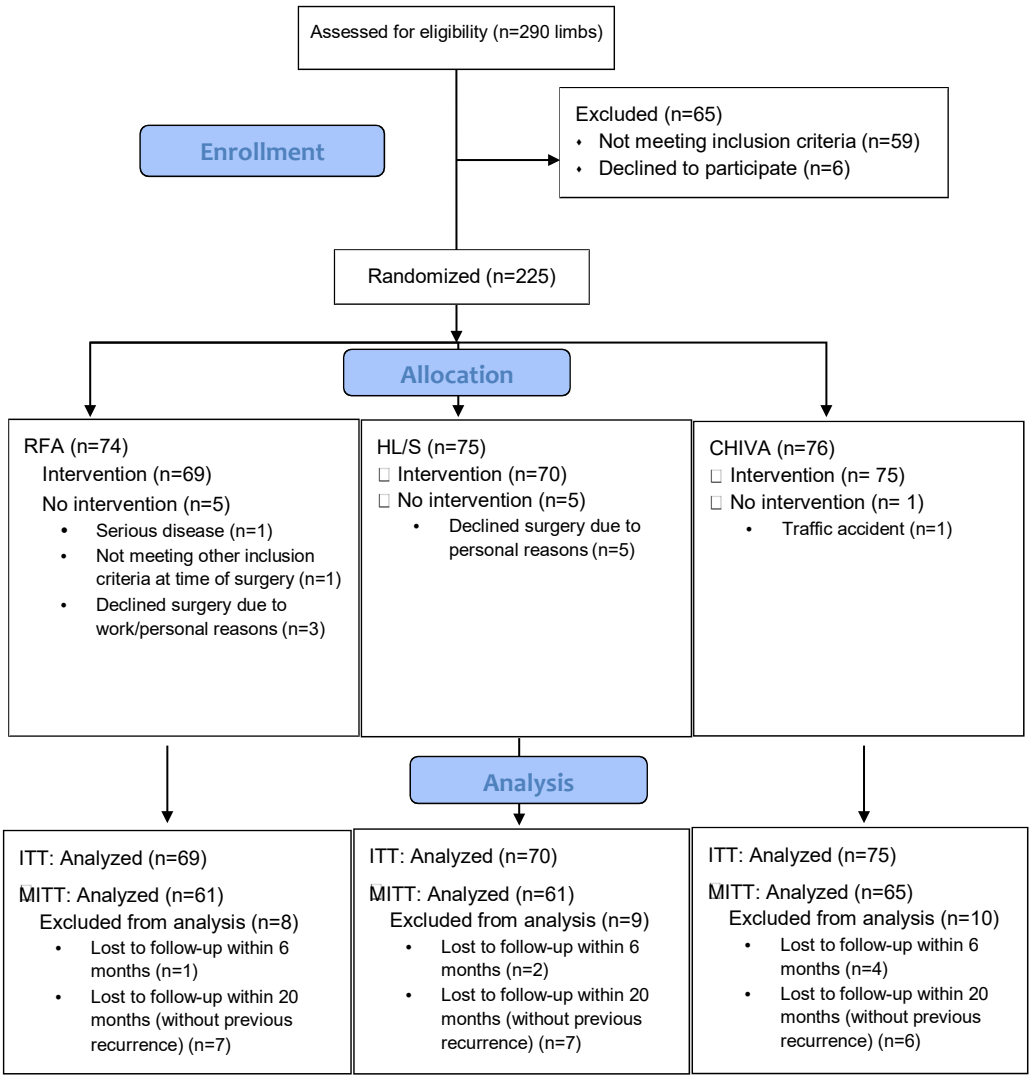

Fig 1. Study flow diagram. *CHIVA,* Conservative hemodynamic cure for venous insufficiency; *HL/S,* high ligation and stripping; *ITT,* intention to treat; *MITT,* modified intention to treat; *RFA,* radiofrequency ablation.

Ethical issues

The present trial was conducted in accordance with the Declaration of Helsinki and good clinical practice principles. The research ethics committee of our center approved the study protocol (October 2012). The protocol was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT02454452). All participants provided written informed consent before any trial-related procedures were performed. The patients were identified by a numeric code, and no personal patient information was included in the study database, preserving the confidentiality of the patients.

RESULTS

From December 2012 to June 2015, a total of 290 limbs were considered eligible and preselected for screening. The analyzed ITT sociodemographic variables, CVD characteristics, and QoL are presented in Table III. More than 80% of the study population were middle-age women with class C2 or C3 CVD. The study flow diagram of the included patients is depicted in Fig 1.

More than 90% of the procedures were performed by the same senior surgeon. The surgical technique was successful in all cases, except for one patient who had been assigned to the RFA group. However, that patient had required the CHIVA technique owing to the impossibility of advancing the catheter into the GSV. Most interventions in the RFA and HLS groups were performed with the patient under general anesthesia (87.9% and 80.9%, respectively). In contrast, in the CHIVA group, 57% of the procedures were performed with the patient under local anesthesia and sedation (40% with general anesthesia and 3% with spinal anesthesia).

Primary endpoint. For the ITT population, the clinical recurrence rate at 24 months was 7.2% (95% CI, 1.1%-13.4%) in the RFA group (5 patients), 4.3% (95%

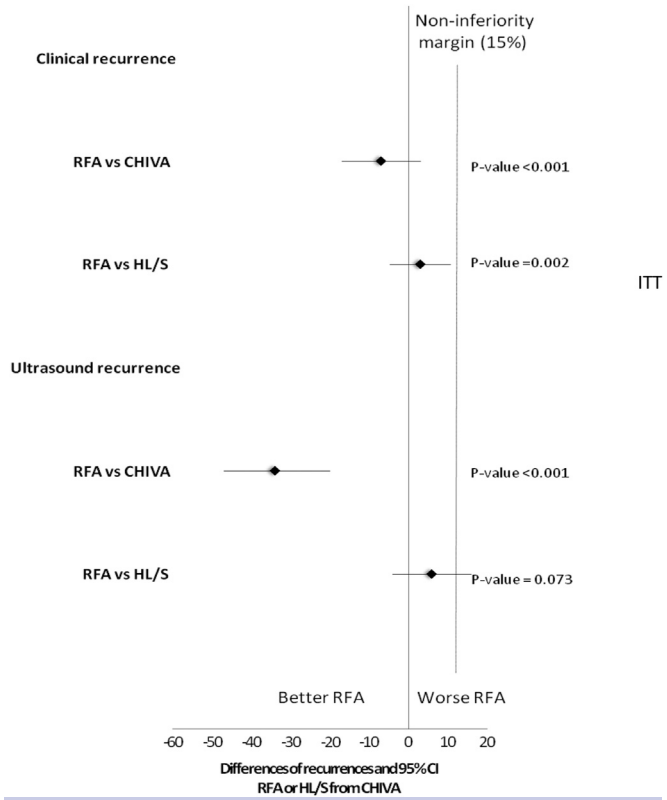

Fig 2. Percentage of differences in clinical and duplex ultrasound recurrence among the three treatments and their 95% confidence intervals (intention to treat population). *CHIVA,* Conservative hemodynamic cure for venous insufficiency; *HL/S,* high ligation and stripping; *RFA,* radiofrequency ablation.

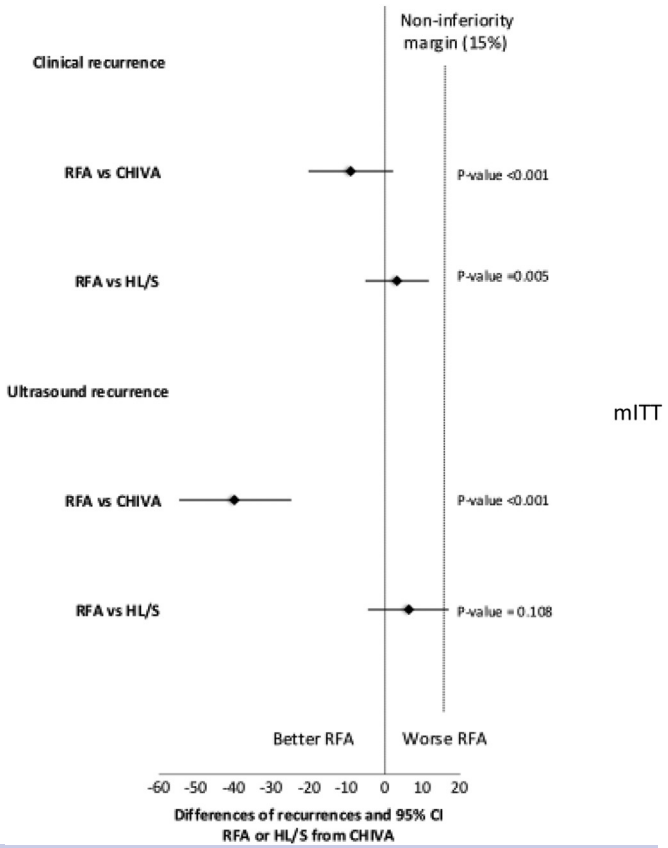

Fig 3. Percentage of differences in clinical and duplex ultrasound recurrence among the three treatments and their 95% confidence intervals (modified intention to treat population). *CHIVA,* Conservative hemodynamic cure for venous insufficiency; *HL/S,* high ligation and stripping; *RFA,* radiofrequency ablation.

CI, −0.5% to 9%) in the HLS group (3 patients), and 14.7% (95% CI, 6.7%-22.7%) in the CHIVA group (11 patients). The comparison of clinical recurrence among the three techniques revealed the following: RFA vs HLS, 2.9% (95% CI, −4.8 to 10.7; noninferiority $P = .002$) and RFA vs CHIVA, −7.5% (95% CI, −17% to 3%; noninferiority $P < .001$). Thus, RFA was noninferior to HLS and CHIVA for clinical recurrence.

Secondary endpoints. DUS recurrence was detected in 5 patients (7.1%; 95% CI, 1.1-13.2), 9 patients (13%; 95% CI, 5.1%-21%), and 35 patients (46.7%; 95% CI, 35.4%-58%) in the HLS, RFA, and CHIVA groups, respectively. Differences in DUS recurrence for the ITT population were as follows: RFA vs HLS, −5.9% (95% CI, −15.9% to 4.1%; noninferiority $P = .073$) and RFA vs CHIVA, 34% (95% CI, 20%-47%; noninferiority $P < .001$). In the HLS group, DUS recurrence had resulted from the presence of residual GSV segments in two patients and neovascularization at the SFJ in three patients. In the RFA group, DUS recurrence had resulted from the presence of a tributary parallel collateral to the GSV in 2 patients, a Hunter perforator in 1 patient, neovascularization owing to incompetent pelvic veins at the SFJ in 1 patient, and an anterior accessory saphenous vein in 1 patient. Four patients had experienced complete recanalization of the GSV. The incidence of DUS recurrence in the RFA group was nearly double that in the HLS group (13% vs 7.1%), and noninferiority could not be established (5.9%; 95% CI, −4.1% to 15.9%; $P = .073$). For the CHIVA group, the cause of DUS recurrence was neovascularization at the SFJ and new pelvic veins in 11 patients and an insufficient GSV without a drainage perforator in 24 patients. Figs 2 and 3 show the different percentages their 95% CIs among the three groups for clinical and DUS recurrence for the ITT and modified ITT populations, respectively.

For DUS recurrence, the hypothesis of noninferiority of RFA compared with HLS could not be confirmed. However, RFA was shown to be noninferior, and even superior, to CHIVA. The interval to clinical and DUS recurrence is shown in Figs 4 and 5. All time to recurrence analyses were superiority tests. The overall log-rank value for clinical recurrence was not statistically significant ($P = .058$). However, the log-rank value between HLS and CHIVA was statistically significant ($P = .031$), in favor of HLS. No

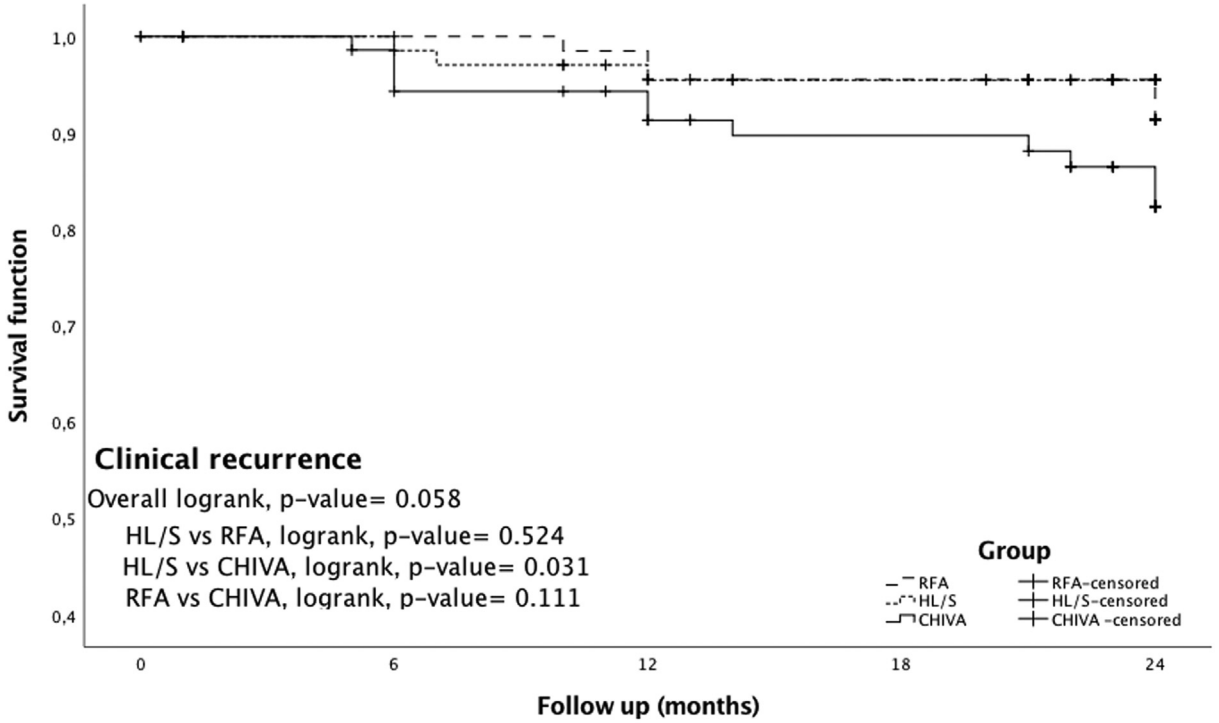

Fig 4. Survival function for clinical recurrence. *CHIVA,* Conservative hemodynamic cure for venous insufficiency; *HL/S,* high ligation and stripping; *RFA,* radiofrequency ablation.

changes in the risk of clinical recurrence were observed in the Cox models (RFA vs HLS: HR, 0.62; 95% CI, 0.15-2.6; $P = .518$; RFA vs CHIVA: HR, 2.29; 95% CI, 0.79-6.58; $P = .126$). In contrast, statistically significant differences were found in the interval to DUS recurrence among the three different techniques ($P < .001$). HLS and RFA showed better results than CHIVA ($P < .001$ for both analyses). However, no differences were observed between HLS and RFA ($P = .321$) in terms of the interval to DUS recurrence. CHIVA resulted in an increase in DUS recurrence (HR, 4.15; 95% CI, 2.0-8.63; $P < .001$). However, no differences were detected between RFA and HLS (HR, 0.59; 95% CI, 0.20-1.75; $P = .073$).

The incidence of postoperative complications is presented in Table IV. The overall incidence of bruising was significantly lower statistically with RFA than with HLS ($P = .009$). No statistically significant differences among the three groups were found for the presence of above the knee hematoma, which was greater in the HLS group (50%) than in the RFA group (41.4%; $P = .054$), nor for any other surgical complication. Only one patient in the HLS group experienced a major complication, DVT associated with PE, which was confirmed by DUS and computed tomography examinations at 1 month postoperatively. The patient was treated with anticoagulation. Two patients with venous ulceration, both randomized to HLS, had experienced complete healing of the ulcer within 1 and 3 months postoperatively, without recurrence. No patient included in the present study had died.

The mean pain score, measured using a VAS on day 1 after surgery, was 38.8 mm (95% CI, 34-43.5 mm), 43 mm (95% CI, 37.2-48.8 mm), and 38.5 mm (95% CI, 33.1-43.8 mm) for the RFA, HLS, and CHIVA groups, respectively. The corresponding mean VAS scores for pain had decreased after 1 month to 26.6 mm (95% CI, 20.9-32.3 mm), 24.7 mm (95% CI, 19.7-29.7 mm), and 26.4 mm (95% CI, 21.2-31.7 mm), with no statistically significant differences. Hyperpigmentation in the ablated area 6 months after surgery was observed in six RFA patients, but had only persisted in three patients at the end of the follow-up period.

No differences were found among the three groups when assessing the clinical response according to the VCSS at 6 and 24 months postoperatively. Statistically significant improvements ($P < .05$) in QoL compared with baseline were found in the three groups using CIVIQ and in the RFA and HLS groups using the SF-36 physical and mental component scores. The changes from baseline in the CIVIQ and SF-36 scores at different postoperative points are shown in Table V. No significant differences in the outcomes among the three groups were observed.

In the RFA group, the preoperative GSV diameter was 6.9 mm (95% CI, 6.4-7.4 mm), which had decreased by ≤2.6 mm (95% CI, 2.3-3.0 mm) at 24 months. The patients with clinical recurrence had had a preoperative GSV of 6.8 mm (95% CI, 4-9.5 mm), with a decrease to 4.1 mm (95% CI, 3.2-4.9 mm) at 24 months. In the CHIVA group,

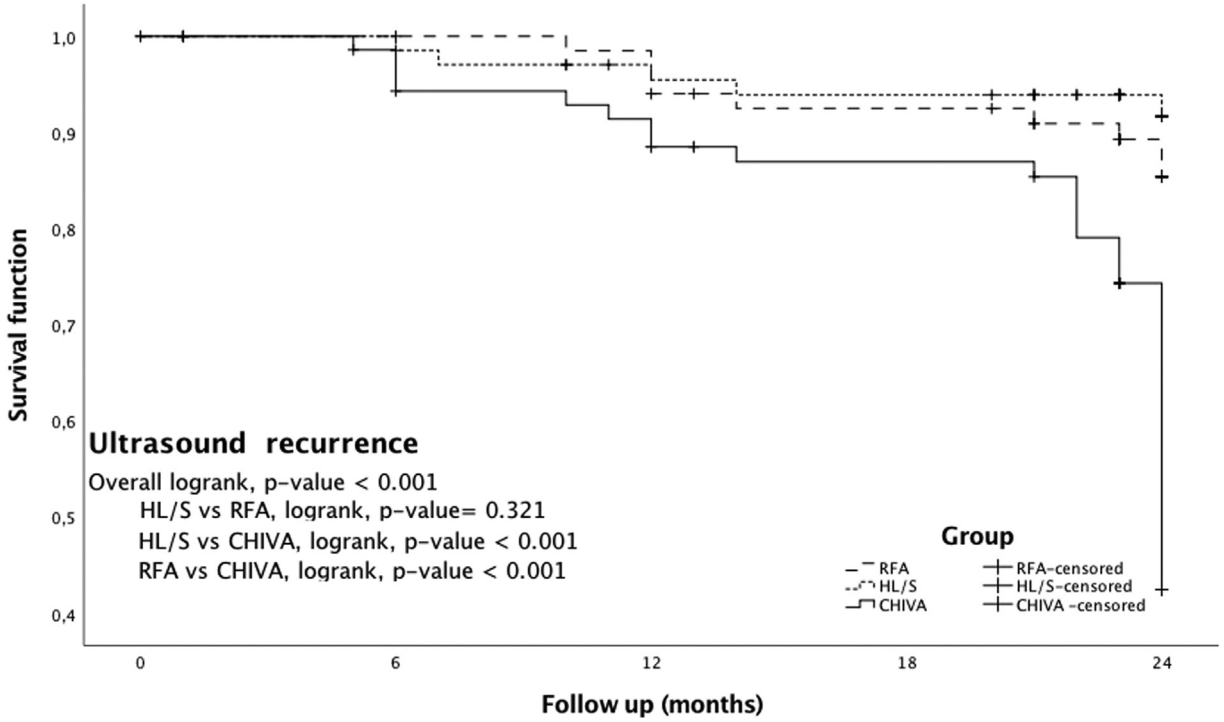

Fig 5. Survival function for ultrasound recurrence. *CHIVA,* Conservative hemodynamic cure for venous insufficiency; *HL/S,* high ligation and stripping; *RFA,* radiofrequency ablation.

a decrease in the GSV diameter was also observed in the patients without clinical recurrence from 6.6 mm (95% CI, 6.2-7 mm) to 3.8 mm (95% CI, 3.5-4.2 mm) postoperatively. Overall, in the case of clinical recurrence, the GSV diameter had decreased from 6.5 mm (95% CI, 5.5-5 mm) to 5 mm (95% CI, 3.8-6.1 mm).

DISCUSSION

Recurrent VVs after conventional surgery is a complex and frequent problem that has remained a challenge to treat. The REVAS group developed a classification for patients with recurrent VVs after surgery that includes true recurrences, residual refluxing veins, and VVs caused by disease progression.[8]

In a systematic review of the Cochrane Library, the recurrence rate at 5 years was reported to be 20% to 28% after HLS and 7% after endovenous thermal ablation treatment at 2 years.[19] In our study, the clinical recurrence rate at 2 years in the HLS, RFA, and CHIVA groups was 4.3%, 7.2%, and 14.7%, respectively.

The primary causes of recurrence after surgery have been tactical or technical errors, neovascularization, and disease progression. Tactical errors can be reduced by performing preoperative DUS scanning, and technical

Table IV. Postoperative complications

Complication	RFA	HLS	CHIVA
Thigh hematoma	24 (41.4)	27 (50)[a]	18 (31)
Bruising	59 (86.8)[b]	68 (98.6)	74 (96.1)
Wound infection	1 (1.5)	4 (5.8)	4 (5.2)
Wound bleeding	21 (30.9)	30 (43.5)	30 (39)
Scar indurations	17 (25)	25 (36.2)	27 (35.1)
Keloid	2 (2.9)	2 (2.9)	0 (0)
Neuritis	12 (17.6)	14 (20.3)	10 (13)
Superficial venous thrombosis	30 (44.1)	28 (40.6)	33 (42.9)
Deep vein thrombosis	0 (0)	1 (1.4)	0 (0)

CHIVA, Conservative hemodynamic cure for venous insufficiency; *HLS,* high ligation and stripping; *RFA,* radiofrequency ablation.
Data are presented as number (%).
[a]HLS vs CHIVA, $P = .054$.
[b]RFA vs HLS, $P = .009$; RFA vs CHIVA, $P = .067$.

Table V. Changes in quality of life-related measures and Venous Clinical Severity Score (*VCSS*)

Variable	RFA	HLS	CHIVA
SF-36			
PCS			
Baseline	72.8 (67.7-77.9)	75.3 (70.5-80.1)	72.7 (67.1-78.3)
24 Months postoperatively	79 (74.1-83.9)	79 (74.5-83.4)	73.7 (68-79.3)
Change	6.2 (12-0.8)[a]	3.6 (8.9-1.6)[a]	1.0 (6.3 to −4.4)
MCS			
Baseline	73.1 (68-78.1)	75.7 (70.5-80.9)	72.9 (67.4-78.4)
24 Months postoperatively	79.8 (75.2-84.4)	82 (77.9-86.1)	75 (69.6-80.4)
Change	6.7 (11-2.1)[a]	6.3 (12-0.6)[a]	2.1 (7.3 to −3.1)[b]
CIVIQ			
Baseline	43.9 (39.6-48.2)	43.3 (39.5-47.1)	43.0 (39.4-46.6)
24 Months postoperatively	34.9 (31.5-38.3)	34.7 (31.6-37.7)	36.5 (32.7-40.2)
Change	−9.0 (−5.2 to −12.9)[a]	−8.6 (−5.3 to −11.9)[a]	−8.3 (−3.1 to −9.9)[a]
Postoperative VCSS[c]			
6 Months	3 (2.3-3.8)	3.1 (2.5-3.8)	3.3 (2.6-4)
24 Months	2.7 (2.1-3.3)	2.1 (1.6-2.6)	2.3 (1.8-2.9)

CHIVA, Conservative hemodynamic cure for venous insufficiency; *CIVIQ*, chronic venous insufficiency quality of life questionnaire; *HLS*, high ligation and stripping; *MCS*, mental component score; *PCS*, physical component score; *RFA*, radiofrequency ablation; *SF-36*, 36-item short-form survey. Data are presented as mean (95% confidence interval).
[a] $P < .05$ for differences from baseline scores at 24 months postoperatively.
[b] $P < .05$ for differences between HLS and CHIVA.
[c] Baseline scores were not registered.

errors depend on surgical skills. Although the causes of recurrent VVs after HLS have varied, failure to strip represents a technical error, and inguinal access could induce neovascularization in the groin.[22] In contrast, a detailed DUS study found that 65% of recurrences after HLS of the GSV had mainly resulted from other causes such as incompetent thigh or calf perforators and pelvic veins.[23] Recurrences after HLS in our sample had resulted from neovascularization at the SFJ (3 patients) and incomplete elimination of reflux caused by the presence of a tributary parallel collateral to the GSV (2 patients).

RFA could lead to less neovascularization as a cause of recurrence because it does not access the groin. GSV recanalization after RFA has often been reported as a failure. However, several studies have suggested that it does not necessarily result in clinical recurrence or symptomatic incompetence. DUS scanning can detect patent reflux of the GSV after RFA in the absence of clinical signs. In the present study, a slight reflux and substantial thickening of the treated GSV wall was detected but without clinical recurrence.

The rates of neovascularization after RFA reported by different investigators have been quite inconsistent.[19] Whiteley et al[24] demonstrated disease progression and de novo reflux in previously normal veins as the main cause of clinical recurrence in patients treated with RFA at 15 years. Other investigators found clinical recurrence rates after RFA of 11% to 15% at 2 to 3 years.[25-28]

More tactical errors might have occurred with the CHIVA technique in our study because all patients required an individualized strategy. In contrast, RFA or HLS involves complete closure of the GSV or removal of the vein; therefore, no tactical errors could have occurred. Parés et al[14] reported a lower rate of clinical recurrence at 5 years with CHIVA than with DUS-guided stripping (31.1% vs 47.9%, odds ratio, 2.01; 95% CI, 1.34-3.00; $P < .001$). In their study, the prevalence of type III (58.4%), type I (16.3%), and type V (12%) shunts differed from our percentages. Despite the different follow-up periods between the study by Parés et al[14] and ours, the great difference in clinical recurrence rates should be pointed out: 4.7% at 5 years vs 14.7% at 2 years.

The overall complication rates with primary GSV surgery have ranged from 17% to 20%.[19] These have typically included wound hematoma and/or infection, lymphatic leakage, femoral vein or artery injury, and neurologic complications. RFA has resulted in an overall lower complication rate. However, in our study, only the incidence of bruising was significantly lower statistically for RFA compared with HLS. Minor complications such as hematoma are relatively common after RFA; however, their relationship to the procedure remains unclear, because RFA will usually be performed with concomitant phlebectomy. In our sample, the high incidence of hematoma might have been related to the

postoperative use of heparin. However, all hematomas had resolved spontaneously. Although 16% of our sample did not present with preoperative symptoms, most of them had had advanced CVD with a CEAP classification of C3 or C4 and had a high risk of progression and complications related to CVD. The assessment of health-related QoL for patients with CVD is also important to evaluate the treatment benefits. Clinical practice guidelines have recommended using patient-reported QoL to assess the outcomes of different treatments.[19] In our sample, although the changes in QoL measured using the SF-36 are inconsistent, the scores obtained using the CIVIQ showed similar improvements for all techniques and all patients.[20] In line with other investigators,[3,28] our findings have confirmed the overall improvement in QoL, with no differences among the three groups at 24 months. Moreover, for patients without preoperative symptoms, the QoL at 24 months only showed statistically significantly improvement in the RFA group.

Study limitations. The present trial established 80% power to assess noninferiority, which could be considered statistically low. Comparing different surgical techniques with different DUS recurrence criteria could also have added a possible bias to the present study. In our study, general anesthesia was used for the RFA procedure, unlike other countries that have favored local and/or tumescent anesthesia. In addition, blinding to the treatment used was not feasible. Observer bias could have occurred, because the surgical method can be deduced from the type of scar, and the type of surgery performed can easily be guessed when assessing DUS scans. Also, the study was performed at one surgical center, and most patients had been treated by one experienced surgeon. Although this reinforces the internal validity of the present study, it could have compromised its external validity, limiting the extrapolation of results to other types of patients and surgical centers. Finally, despite our efforts to monitor up patients according to the calendar established in the study protocol, 12.6% of patients could not be assessed at 24 months (with losses homogenously distributed among the three groups).

CONCLUSIONS

The results from the present trial support the increasing use of RFA in the setting of concomitant phlebectomy to treat lower extremity VVs due to GSV incompetence, not only for its safety, but also for its efficacy at the mid-term follow-up point. RFA was proved to be noninferior in terms of clinical recurrence compared with HLS of the GSV and the CHIVA technique. Our findings have confirmed the hypothesis of noninferiority of RFA, although no clear advantages in terms of complications were found.

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AUTHOR CONTRIBUTIONS

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