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**Article** *in* International angiology: a journal of the International Union of Angiology · February 2022

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ORIGINAL ARTICLE
VENOUS DISEASE

EDITOR'S CHOICE

# A prospective multicenter randomized clinical trial comparing endovenous laser ablation, using a 1470 nm diode laser in combination with a Tulip-Tip™ fiber *versus* radiofrequency (Closure FAST™ VNUS®), in the treatment of primary varicose veins

Anne-Cathérine KEMPENEERS [1] *, Beate BECHTER-HUGL [2], Sarah THOMIS [2], Daphne van den BUSSCHE [3], Marc E. VUYLSTEKE [3], Mathieu M. VUYLSTEKE [4]

[1]Department of General Surgery, Faculty of Medicine, Catholic University of Leuven, Leuven, Belgium; [2]Department of Vascular Surgery, University Hospitals of Leuven, Leuven, Belgium; [3]Department of Vascular Surgery, Sint-Andries Ziekenhuis, Tielt, Belgium; [4]Department of European Economics, College of Europe, Bruges, Belgium

*Corresponding author: Anne-Cathérine Kempeneers, Department of General Surgery, Catholic University of Leuven, Leuven, Belgium. E-mail: annecatherine.kempeneers@student.kuleuven.be

## ABSTRACT

**Background:** The treatment of chronic venous disease, has largely shifted from high ligation and stripping to endovenous thermal ablation (EVTA) techniques, because of its comparable efficacy and lack of invasiveness. This clinical trial aimed to compare the efficacy of two thermal ablation techniques, endovenous laser ablation (EVLA) 1470-nm with Tulip-Tip™ fiber and radiofrequency ablation (RFA) ClosureFastTM using a non-inferiority design for occlusion rate (primary outcome).

**Methods:** A prospective multicenter randomized clinical trial randomized 280 patients for the treatment of great saphenous vein (GSV) reflux. Primary outcome was the GSV occlusion rate, secondary outcome factors were the possible side-effects of the treatment such as pain, ecchymosis, quality of Life (CIVIQ-20), revised Venous Clinical Severity Score (r-VCSS). One-year follow-up period.

**Results:** The total occlusion rates at one year follow-up were 96.4% and 94.5% in the EVLA and RFA groups respectively (P=0.15). Regarding secondary outcomes, such as postoperative CIVIQ-20, r-VCSS, analgesia, absenteeism, there was no significant difference between both treatment groups.

**Conclusions:** RFA and EVLA, using a 1470 nm laser with Tulip-Tip™ fiber, of the GSV results in equal occlusion rates at one year, with comparable postoperative pain and improved quality of life.

(*Cite this article as:* Kempeneers AC, Bechter-Hugl B, Thomis S, van den Bussche D, Vuylsteke ME, Vuylsteke MM. A prospective multicenter randomized clinical trial comparing endovenous laser ablation, using a 1470 nm diode laser in combination with a Tulip-Tip™ fiber *versus* radiofrequency (Closure FAST™ VNUS®), in the treatment of primary varicose veins. Int Angiol 2022;41:322-31. DOI: 10.23736/S0392-9590.22.04747-2)

**Key words:** Laser ablation; Radiofrequency ablation; Varicose veins; Prospective studies; Pain, postoperative.

Chronic venous disease (CVD) of the lower extremities is a common disorder with a worldwide prevalence of 83.6 per cent clinical etiologic anatomic pathophysiologic (CEAP) class C0s to C6) (Table I).[1, 2] The prevalence of CVD differs geographically, but is higher in developed countries.[2]

An epidemiological survey of 6009 adults in Belgium and Luxembourg found an overall prevalence as high as 61.3% for CVD (CEAP class C1-C6), and 25% for chronic venous insufficiency (CVI) comprising CEAP class C3-C6.[3] The Bonn Vein Study, a population-based study conducted in Germany, showed prevalence of 90.4% and 17.1% for CVD and CVI respectively.[4]

Patients with CVD present with a variety of symptoms (leg pain, discomfort, heaviness, nocturnal cramps etc.) and signs (varicose veins, edema, skin discoloration, venous ulceration etc.), that considerably impact their quality of life. Prevalence, disease severity, and treatment requirements all increase with age.[4, 5]

Varicose veins (VVs) of the legs, which are a common sign of venous insufficiency, affect around one third of the adult population.[6-8] In three out of four cases of varicose disease, reflux of the great saphenous vein (GSV) is the underlying cause.[9, 10] Treatment of VVs aims to reduce symptoms of CVD and thereby to improve quality of life, but also to prevent long-term complications of CVI such as leg ulceration.[11]

Endovenous techniques became very popular as a minimal invasive alternative treatment to obtain ablation of incompetent saphenous veins.[12] Essentially, these can be divided into two categories: thermal and non-thermal techniques. Two of the most frequently used, endovenous laser and radiofrequency ablation (EVLA and RFA), are both thermal techniques.[13]

Meta-analyses show that EVLA and RFA are as effective as classical surgery (high ligation and stripping) in treatment of GSV insufficiency.[14, 15] Previous data showed a 1-year occlusion rate of 95.7 percent with RFA[14] and 97 percent with EVLA.[16, 17]

Moreover, patients treated with endovenous thermal ablation (EVTA) have less postoperative pain, swelling and bruising, and a shorter duration of postoperative disability compared to surgery.[13, 18] EVTA has been recommended as the treatment of choice for saphenous vein incompetence by several international guidelines.[13-15]

Several studies have gone on to compare different modalities of these two treatments. For example, a 980-nm diode laser for EVLA is associated with more postoperative pain and it has therefore been replaced by the use of 1470-1500 nm lasers.[17, 19] A comparative prospective cohort study showed similar GSV obliteration rates and clinical effectiveness in the long term after RFA by ClosureFast™ and 1470-nm EVLA with a radial-tip fiber (RTF). There was no difference in postoperative pain scores between the two groups.[20]

In addition to choice of wavelength, many different types of fiber tips have been developed and compared.[21] Although all tips have proven to be effective in occluding the incompetent vein, they differ in side effect profile. We have chosen the Tulip-Tip™ fiber, which is regarded as a safety tip fiber. The Tulip-tip fiber consists of a bare laser fiber with a hollow tube at its distal end. This tube has tulip-shaped, self-expandable blades scattered around the fibers end. The blades push away the vein wall, avoiding therefore direct contact and heat transfer between the laser fiber and the vein wall. This geometric restraint prevents vein wall perforations and associated postoperative adverse effects. Moreover, as the tulip petals are of low stiffness, the tip tends to be centered in the middle of the vein, creating a more ideal spatial pattern of irradiation.

The primary objective of this study was to compare two thermal ablation techniques, EVLA and RFA, in terms of anatomical success (primary outcome) and postoperative side-effects (secondary outcome). To that end, a single-blind, two-arm parallel randomized control trial (RCT) was set up comparing the efficacy of EVLA and RFA, with the hypothesis that EVLA would be non-inferior to RFA regarding occlusion rates and possible side-effects.

The specific EVLA modalities in this study were a safety fibre tip, the Tulip-Tip™ fiber in combination with a 1470-nm wavelength laser.[22]

Table I.—*Clinical-Etiology-Anatomy Classification for chronic venous disorders.*[1]

| C classes in CEAP | Clinical manifestation |
|---|---|
| C0 | No visible or palpable signs of venous disease |
| C1 | Telangiectasias or reticular veins |
| C2 | Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more |
| C3 | Oedema |
| C4a | Pigmentation or eczema |
| C4b | Lipodermatosclerosis or *atrophie blanche* |
| C5 | Healed venous ulcer |
| C6 | Active venous ulcer |

The original Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification for chronic venous disorders (CVD) was developed in 1993 and revised by 2004.

## Materials and methods

A multicenter, prospective, single-blind, two-arm parallel group, non-inferiority RCT was carried out at the Depart-

ment of Vascular Surgery at the Sint-Andriesziekenhuis in Tielt and the University Hospitals in Leuven between February 2013 and September 2018.

The protocol was reviewed and approved by the Ethics Committee of Ghent University Hospital and the local research committee of Sint-Andries hospital (Tielt). The trial was carried out in accordance with the guidelines defined in the Declaration of Helsinki.

The study was registered at www.clinicaltrials.gov (registration number NCT01722019).

Patients attending the vascular outpatient clinic on the two study sites, were evaluated for eligibility, based on medical history, clinical examination and DUS.

Adult patients (aged between 18 and 75 years) who had a symptomatic incompetent GSV, with functional and/ or aesthetic inconvenience, were eligible to participate. Diagnosis of venous insufficiency was always made by clinical evaluation (CEAP ranging from 2 to 6) and Duplex ultrasound scanning (DUS). See Table II for an overview of inclusion and exclusion criteria. Patients who met these inclusion criteria were invited to enroll in the study. All patients gave written informed consent.

The participating patients were randomized to either EVLA or RFA, respectively using a 1470-nm diode laser with Tulip-Tip™ fiber (Tobrix®, Waalre, The Netherlands) and ClosureFast™ (VNUS® Med Tech, San Jose, CA, USA) device, with an allocation ratio of 1:1, using numbered and sealed envelopes. Four physicians (all vascular surgeons) performed the interventions. Patients and ultrasound technicians were blinded to the treatment modality. Patients filled in the questionnaires on their disease-specific quality-of-life, postoperative pain and analgesic intake in the absence of the treating consultant. Follow-up was organized at 5 days, 1 month, six months and 1 year post treatment. The physician who evaluated the patient at follow-up visit was not different from one who treated the patient, and was by consequence aware of the technique used.

## Techniques

Preoperatively, detailed duplex ultrasound mapping and assessment of the superficial, deep venous and perforator systems were conducted in standing position. The diameter of the GSV was assessed at three points: proximal (2 cm distal to the saphenofemoral junction [SFJ]), medial (mid-thigh) and distal (knee). From these measurement points, the average vein diameter was calculated. Mapping of insufficient tributaries and perforator veins was marked on the skin.

For both EVTA techniques, the GSV was punctured under DUS guidance at the most distal point of GSV incompetence. Once venous access was obtained, a guide wire was passed through the needle up to the SFJ, over which an introducer sheath was then passed. After removing the guide wire, either the laser or RFA fiber/catheter was positioned approximately 1-2 cm distal to the SFJ, at the ostium of the epigastric vein. Correct positioning was verified by intraoperative ultrasound. Technical details of both procedures have been described elsewhere.[16, 22, 23]

Prior to EVTA, tumescent anesthetic (20 ml lidocaine 1 per cent diluted in 500 mL sodium bicarbonate 1.4 per cent) was delivered along the length of the GSV. This was

Table II.—*Overview of inclusion and exclusion criteria.*

| Inclusion criteria | Exclusion criteria |
|---|---|
| Adult patients (aged between 18 and 75 years), who had symptomatic insufficient GSV, *i.e.* functional and/or aesthetic inconvenience | • Proven peripheral arterial disease (ankle: brachial pressure index below 0.8 or known PAD) |
| Diagnosis of venous insufficiency was always made by clinical evaluation (CEAP between 2 and 6) and duplex ultrasound scanning (DUS). | • Deep vein insufficiency or thrombosis (ultrasound proven) |
| Unilateral treatments of the GSV | • Klippel-Trenaunay Syndrome |
| GSV diameter not exceeding 20 mm | • Cross dilation with two or more insufficient side branches |
| | • Cross insufficiency of AASV |
| | • Severe hepatic insufficiency (contra-indication for local tumescent anesthesia) |
| | • History of surgical or endovenous treatment of the GSV or SSV |
| | • BMI 35kg/m$^2$ |
| | • Oncological disease less than one year ago<br>• Bilateral treatments<br>• Concomitant incompetence of the AASV and/or SSV |
| | • Pregnancy, lactation and women less than three months after childbirth |

GSV: great saphenous vein; AASV: anterior accessory saphenous vein; SSV: small saphenous vein.

done under ultrasound guidance using a mechanical infusion pump.

The EVLA catheter, a 1470-nm diode laser with a Tulip-Tip™ fiber, was withdrawn in a controlled, continuous technique at 1 mm/s, guided by signals from the generator. We use the term linear endovenous energy deposit (LEED) to refer to the amount of energy in Joules divided by the treated vein length in centimeters.[24, 25]

The RFA catheter with a 7 cm heating element was pulled back in a segmented manner. The first 7 cm close to the SFJ were treated with two heating cycles of 20 s, whereas the remainder of the GSV received only one cycle.

All patients were treated in Trendelenburg position. Possible tributaries were treated by Muller phlebectomies, but were avoided in the immediate proximity of the ablated GSV. This measure was taken to not alter the result of the endovenous treatment regarding ecchymosis. After both procedures, a strong compression bandage (Tensoplast®) was applied. Patients wore these continuously for the first two/three days. Thereafter, patients were instructed to wear a thigh-high compression stocking (class 2) during the day only for the following two weeks.

Patients received a prescription for Diclofenac 75mg on discharge and were instructed only to take them in case of pain or inflammation in the treated leg, up to a maximum of twice a day. Patients at risk (*e.g.* with a history of deep venous thrombosis (DVT) or superficial thrombophlebitis) were prescribed thromboembolic prophylaxis in the form of low-molecular-weight heparin (LMWH) (enoxaparin 40 mg) for 10 days. Furthermore, patients were advised to mobilize immediately after discharge and to resume work and daily activities as soon as possible.

Clinical follow-up was scheduled at 5 days, 1 month, 6 and 12 months postoperatively.

The primary outcome was the GSV occlusion rate up to one year postoperatively. A Duplex scan was therefore scheduled upon inclusion and also at one month, six month and 12-month follow-up appointments. The modified Groupe d'Évaluation des Lasers et de l'Échographie Vasculaire (mGELEV) score was used to evaluate the shrinkage rate (Table III).[22] This score compares the proximal measured diameter (2 cm distal to the SFJ) of the treated vein pre-, and post-intervention. Duplex controls were carried out by an independent, blinded radiologist or vascular technician.

Secondary outcome measures and their measurement were as follows: 1) clinical signs of CVD and thus disease severity, were evaluated using the CEAP classification at inclusion and the revised Venous Clinical Severity Score (r-VCSS), also at baseline, as well as at each follow-up.[26] 2) Chronic Venous Insufficiency Questionnaire 20 (CIVIQ-20) was used to assess disease-specific QoL before and two weeks after treatment.[27] The questionnaire had to be completed and returned at the next (one month) follow-up visit. 3) Pain was rated using a Visual Analogue Pain Scale (VAS) at five days postoperatively, *i.e.* the first clinical check-up. The second VAS pain score measured the average pain intensity during the first 14 days postoperatively.

Table III.—*Modified GELEV Score.*[22]

| Modified GELEV Score | |
|---|---|
| 0 | No occlusion, refluxing vein, unchanged vein |
| 1 | Partial occlusion with proximal reflux |
| 2 | Partial occlusion without reflux |
| 3 | Complete occlusion with unchanged diameter |
| 4 | Complete occlusion with diameter reduction >30% |
| 5 | Complete occlusion with diameter reduction >50% |
| 6 | Fibrotic cord, vein not visible |

This scoring was introduced by GELEV (Groupe d'Evaluation des Lasers et de l'Echographie Vasculaire), part of the Société Française d'Angiologie.

A question on the level of analgesic intake was asked at each follow-up appointment. Measurement of ecchymosis was done with ecchymosis scoring (surface ecchymosis [cm²] / length of treated vein [cm]) on the fifth postoperative day.

At each follow-up visit, the occurrence of adverse events was recorded: extended hospital stay, DVT, superficial venous thrombosis (SVT), wound infection necessitating drainage, hematoma/ecchymosis, hyperpigmentation, paresthesia, lymphoedema, neuropathy, new venous ulcer. Data analyses were performed by an independent investigator (ACK).

## Statistical analysis

Sample size calculations for this non-inferiority design determined that 216 patients (108 per arm) would be needed to detect a less than 7.5% difference in occlusion rate after one year between EVLA and RFA groups. With a significance level of $\alpha$=0.05 and $\beta$=0.10, 216 patients were required in order to be sure that the upper limit of a one-sided 95 per cent CI (or equivalently a two-sided 90% CI) would exclude the difference in favor of the RFA treatment of more than 7.5% (=$\Delta$ non-inferiority margin). These calculations were done in R 4.0.3 using the "scoresci" function from the "PropCIs" library.

Data were analyzed using per-protocol and as per last-observation-carried-forward (LOCF) methods.

For non-parametric ordinal variables a Mann-Whitney U test or a Kruskal-Wallis Test, and for nominal values a

$\chi^2$ test has been used. For continuous variables we used an Independent Samples *t*-test. Statistical analysis was done using statistical software for Windows® (SPSS®; IBM, Armonk, NY, USA). Statistical analysis was done by an independent economist (MMV).

## Results

A total of 2236 consecutive patients were considered for eligibility between February 2013 and September 2018. Of these, 280 patients (280 legs) met the inclusion criteria and were willing to participate; they were randomized between the two intervention groups. The EVLA and RFA groups comprised 142 and 138 patients respectively and all patients received treatment as intended (Figure 1).

There were no significant differences in the basic demographics and preoperative anatomic and clinical measurements at baseline between the two groups (Table IV).

In the case of the EVLA group, veins were treated with 1470-nm wavelength in the continuous mode at 6 Watt of power. If the average vein diameter exceeded 8 mm, power was increased to 7 Watt. Maintaining a continuous retraction mode at a rate of 1mm/sec, the average LEED was aimed to be between 45 and 60 J/cm. In the EVLA group the average LEED was 55, 13 J/cm. The Closure-FAST catheter with a 7-cm heating element is placed 2 cm from the SFJ. Segmental energy delivery at 120° is delivered in 20-second cycles. The proximal vein is treated with two cycles, followed by one cycle per 7 cm to the remaining

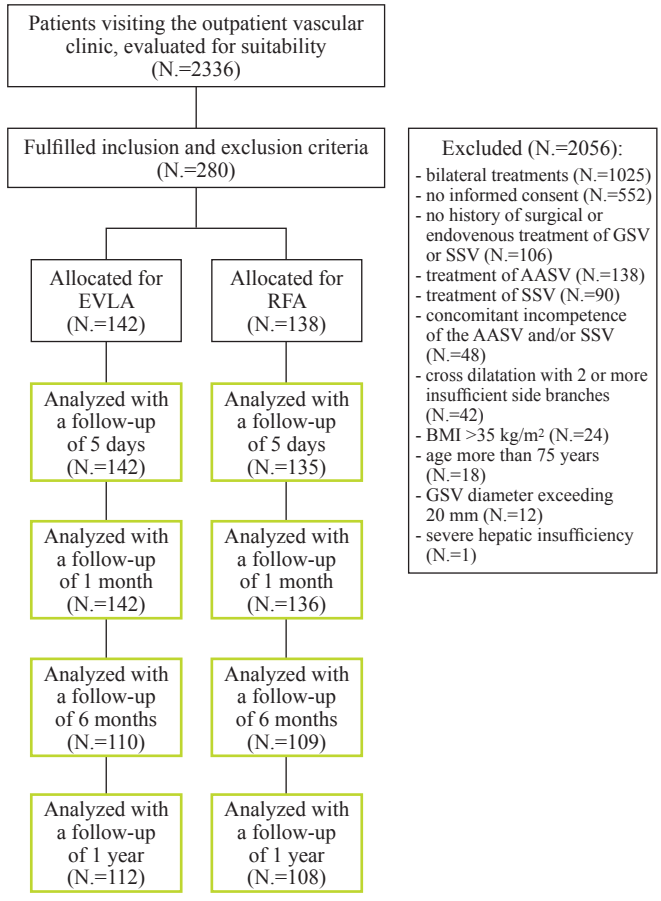

Figure 1.—Consort flow diagram.

TABLE IV.—*Baseline characteristics: demographics and preoperative anatomical and clinical measurements.*

| | EVLA (N.=142) | RFA (N.=138) | P value* |
|---|---|---|---|
| Patient demographics (t-test) | | | |
| Age (years)* | 51.48 (12883) | 51.54 (13173) | 0.969 |
| Sex ratio (F:M) (F%) | 94:48 (66%) | 83:55 (59%) | 0.295 |
| BMI (kg/m²)* | 29296 (15.35) | 29937 (16.59) | 0.739 |
| Limb characteristics | | | |
| Baseline C class (CEAP classification) † | Median: C2 (2-3) | Median: C2 (2-3) | 0.279 |
| C2 | 88 (62%) | 95 (68.9%) | |
| C3 | 20 (14.1%) | 18 (13%) | |
| C4 | 27 (19%) | 20 (14.5%) | |
| C5 | 2 (1.4%) | 5 (3.6%) | |
| C6 | 1 (0.7%) | 0 (0%) | |
| Missing | 4 (2.8%) | 0 (0%) | |
| GSV diameter* (mm) | 6.37 (1.98) | 6.05 (1.83) | 0.165 |
| VCSS* | 5.42 (11.5) | 3.77 (1.78) | 0.097 |
| CIVIQ2* | 33.97 (17.13) | 33.41 (16.201) | 0.781 |
| Treatment characteristics | | | |
| Length of treated vein segment (cm)* | 38.04 (10.48) | 40.32 (10.26) | 0.068 |
| Energy used LEED (J/cm)* | 57.14 (10.28) | / | |

Values are *mean (SD) and †median (IQR).
EVLA: endovenous laser ablation; RFA: radiofrequency ablation; CEAP: Clinical Etiologic Anatomic Pathophysiologic; VCSS: Venous Clinical Severity Score; CIVIQ-2: Chronic Venous Insufficiency Questionnaire 2; GSV: great saphenous vein; LEED: linear endovenous energy density.

distal venous segments. On average patients in the RFA group received 7 cycles.

A total of 277 patients attended five-day follow-up, with 276 (98.6 per cent) at 1-month follow-up, 219 (78.2 per cent) at 6-months follow-up and 220 (78.6 per cent) attending 1-year follow-up.

All 280 patients were included in a sensitivity analysis for the primary outcome (occlusion rate), in which the missing values at 12 months were imputed with the value at 6 months (if available), using the last-observation-carried-forward (LOCF) method. For per-protocol (PP) analyses, a total of 220 patients were analyzed; 60 did not complete the 1-year follow-up due to loss to follow-up.

## Primary outcome measures

The GSV was completely occluded or absent (fibrotic cord) in 108 (96.4%) of 142 patients and 102 (94.5%) of 138, 1 year after EVLA and RFA respectively (Figure 2). The GSV was partially or not occluded in four patients and in six patients in the respective groups. Both EVLA and RFA had comparable success rates (P=0.15). There were respectively 30 and 30 patients lost to follow-up in the EVLA and RFA groups at 1 year.

Results for the LOCF analyses were comparable, with occlusion rates of 96.7 and 94.2 per cent for EVLA and RFA respectively (P=0.154) (Table V).

The evolution of occlusion, displayed as mean mGELEV score, is depicted in Figure 3.

See Supplementary Digital Material 1, Supplementary Table I for descriptive table of mGELEV scores at each follow-up.

## Secondary outcome measures

At baseline, there were no significant differences in median r-VCCS and CIVIQ-20 between the groups. At 6-month follow-up, in the PP analysis, the r-VCSS had improved to a median of 1 for both treatments, which continued up to 12 months. This improvement was statistically significant for both EVLA and RFA (P<0.001) (Figure 4).

At 1-month follow-up, the disease-specific QoL according to CIVIQ-20 had improved from a median of 27 to 23 in the EVLA group and 25.5 to 22 in RFA group.

There were no significant differences between both treatment groups at any of the follow-ups, nor for r-VCSS or CIVIQ-20 scores (Table VI).

VAS scores reported by patients during the first 5 days and 14 days after treatment showed the same pattern in both groups. Patients reported an initially low pain score

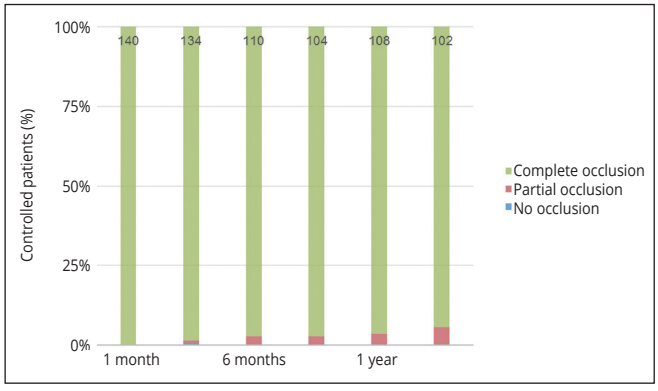


Figure 2.—Occlusion rate of the great saphenous vein.

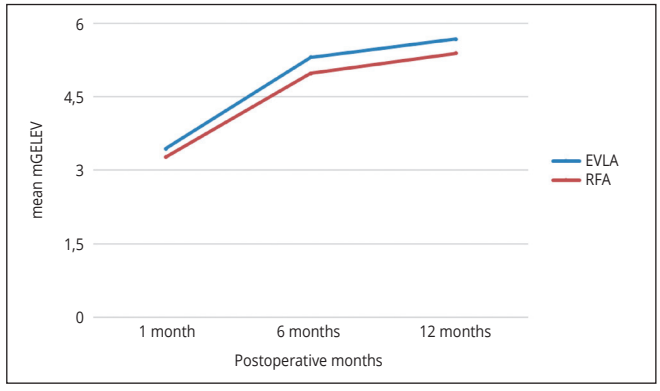


Figure 3.—Evolution of the occlusion of the great saphenous vein.

TABLE V.—*Primary outcome measure: occlusion of great saphenous vein using mGELEV Score.*

| | 1 month | | 6 months | | 1 year PP | | 1 year LOCF | |
|---|---|---|---|---|---|---|---|---|
| | EVLA N.=140 | RFA N.=135 | EVLA N.=113 | RFA N.=106 | EVLA N.=112 | RFA N.=108 | EVLA N.=124 | RFA N.=120 |
| Complete occlusion | 140 (100) | 134 (98.5) | 110 (97.3) | 103 (96.2) | 108 (96.4) | 102 (94.5) | 120 (96.7) | 113 (94.2) |
| No occlusion / partial occlusion | 0 (0) | 2 (1.5) | 3 (2.7) | 3 (3.8) | 4 (3.6) | 6 (5.5) | 4 (3.3) | 7 (5.8) |
| | P=0.153 | | P=0.176 | | P=0.150 | | P>0.05 | |

No significant differences between EVLA and RFA groups at each follow-up. Values in parentheses are percentages. For nominal values a $\chi^2$ test has been used.
mGELEV 0=no occlusion; mGELEV 1,2=partial occlusion; mGELEV 3,4,5,6=complete occlusion.
EVLA: endovenous laser ablation; RFA: radiofrequency ablation; PP: per-protocol; LOCF: last-observation-carried-forward.

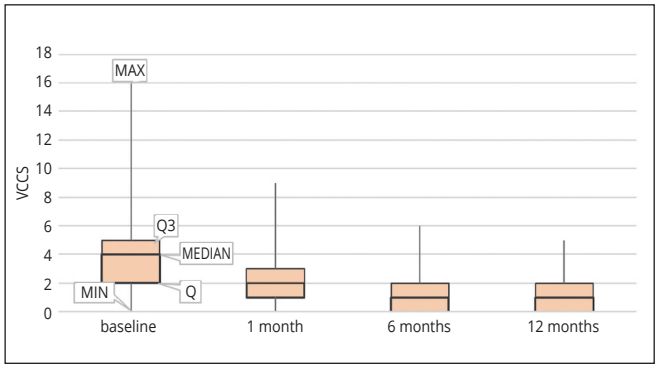


Figure 4.—Disease severity.

Table VI.—*Per-Protocol Analysis of revised Venous Clinical Severity Score and Chronic Venous Insufficiency Questionnaire-20.*

| | EVLA (N.=142) | RFA (N.=138) | P value* |
|---|---|---|---|
| r-VCSS† | | | |
| Baseline | 4 (2-5) | 4 (2-5) | 0.381 |
| 1 month | 2 (1-3) | 2 (1-3) | 0.521 |
| 6 months | 1 (0-2.25) | 1 (0-2) | 0.469 |
| 12 months | 1 (0-2) | 1 (0-2) | 0.941 |
| Changes in r-VCSS baseline *versus* 12 months | P<0.001 | P<0.001 | |
| CIVIQ-20† | | | |
| Baseline | 27 (25-30.75) | 25.5 (23-31) | 0.667 |
| 1 month | 23 (20-25) | 22 (20-24) | 0.394 |

No significant differences between both treatment groups at any of the follow-ups, nor for VCSS or CIVIQ-2 scores. Significant evolution in r-VCSS scores 12 months after treatment for both EVLA and RFA.
†Values are median (IQR).
EVLA: endovenous laser ablation; RFA: radiofrequency ablation; r-VCSS: revised Venous Clinical Severity Score; CIVIQ-20: Chronic Venous Insufficiency Questionnaire 20.

with a mean (SD) of 1.8 (1.33) and 1.46 (1.42) in the EVLA and RFA group respectively. After two weeks, pain scores slightly increased over time to 2.24 (1.68) and 1.88 (1.49), respectively. Comparing the scores of the groups, there was only a marginal significant difference between EVLA and RFA during the first five days (P=0.04).

Use of analgesics for EVLA and RFA was however comparable with a mean number of 1.65 and 2.12 days respectively (P=0.535) (Table VII).

The median duration of sick leave was four days (range 1-7.5) after EVLA and three days (range 0 -7) after RFA (p=0.79). However, patients returned to daily activities after two (range 1-5) days in both groups (median value). Patient satisfaction, accessed in the questionnaire two weeks after treatment, was likewise comparable with a mean satisfaction score of 8.89 for EVLA and 9.00 for RFA (P=0.59) (Table VII).

Table VII.—*Secondary outcome measures (pain, use of analgesics, absenteeism, patient satisfaction) according to treatment group.*

| | EVLA (N.=142) | RFA (N.=138) | P value |
|---|---|---|---|
| Pain | | | |
| VAS (first 5 days)* | 1.8 (1.33) | 1.46 (1.42) | 0.04 |
| VAS (first 14 days)* | 2.24 (1.68) | 1.88 (1.49) | 0.061 |
| Use of analgesics* (days) | 1.65 (8.59) | 2.12 (11.86) | 0.535 |
| Absenteeism | | | |
| Return to work† (days) | 4 (1-7.5) | 3 (0-7) | 0.787 |
| Return to daily activities† (days) | 2 (1-5) | 2 (1-5) | 0.997 |
| Patient satisfaction* | 8.89 (1.43) | 9.00 (1.37) | 0.588 |

Values are *mean (SD) and †median (IQR).
EVLA: endovenous laser ablation; RFA: radiofrequency ablation; VAS: Visual Analogue Scale.

Table VIII.—*Adverse events according to treatment group.*

| | EVLA (N.=142) | RFA (N.=138) | |
|---|---|---|---|
| Ecchymosis | | | |
| 5 days | 21/142 (14.8) | 21/135 (15.6)?? | |
| Ecchymosis score* | 0.339 (2.871) | 0.749 (6.198) | P=0.0474 |
| 1 month | 8/139 (5.8) | 10/133 (7.5) | |
| 6 months | 1/108 (0.9) | 2/113 (1.8) | |
| 12 months | 0/110 | 0/106 | |
| Hyperpigmentation | | | |
| 1 month | 13/139 (9.4) | 20/133 (15) | |
| 6 months | 13/113 (11.5) | 19/109 (17.4) | |
| 12 months | 5/110 (4.5) | 13/106 (12.3) | |
| paresthesia | | | |
| 12 months | 1/110 | 1/106 | |
| DVT | None | None | |

Values in parentheses are percentages and values* are mean (SD).
EVLA: endovenous laser ablation; RFA: radiofrequency ablation; DVT: deep venous thrombosis. Ecchymosis score=surface ecchymosis ($cm^2$)/length of treated vein (cm).

## Adverse events

The incidence of adverse events was registered at all check-ups (Table VIII).

Ecchymosis, another common side effect occurring shortly after EVTA treatment, was reported in 14.8% of patients from the EVLA group and in 15.6% of patients from the RFA group after 5 days.

Quantification of ecchymosis on the fifth postoperative day was scored 0.339 (2871) and 0.749 (6.198) (P=0.0474) (surface ecchymosis [$cm^2$]/length of treated vein [cm]) mean (SD) value for EVLA and RFA respectively. Bruising, typically transient in nature, more than halved after one month (to 5.8% and 7.5% respectively), at six months it showed a further decline to 1.8% and 0.9%, and was no longer present in either of the groups at one-year follow-up.

Skin hyperpigmentation, on the other hand, became apparent within the first month after treatment, affecting 13

of 139 (9.4%) and 20 of 133 (15%) patients reviewed in the EVLA and RFA groups respectively. The pigmentation decreased over time, and still affected five of 110 (4.5%) and 13 of 106 (12.3%) patients reviewed one year after treatment. The evolution of hyperpigmentation was carefully monitored during follow-up. Observation showed that it usually concerned a small area just proximal to the knee, where the GSV is known to run very superficially. Precipitation of hemosiderin causes hyperpigmentation. Over time intensity and occurrence of pigmentation decreases. In 17% of patients remaining in follow-up, it was still visible after one year.

Paresthesia was reported in two patients, both in the EVLA group, one year after treatment.

No major complications such as DVT or pulmonary embolism were reported.

## Discussion

EVTA techniques have largely replaced high ligation and stripping in the treatment of chronic venous disease, due to their comparable efficacy and lack of invasiveness. The most commonly used techniques, radiofrequency and laser ablation, have been compared with each other in several studies. However, there is still no general consensus on which technique is superior. This two-center prospective RCT compared the efficacy of two thermal ablation techniques, RFA (ClosureFAST™) and EVLA (1470-nm diode laser with Tulip-Tip™ fiber), for primary GSV insufficiency. EVLA proved to be non-inferior to RFA (P=0.15) and thus at least as efficacious when considering GSV occlusion rates at one year follow-up. We computed one-year ablation rates of 96.4% and 94.5% in the EVLA and RFA groups respectively, using per-protocol analysis.

Recanalization of the GSV after EVTA is reported in up to 10 per cent of patients after one year.[28] There are several independent prognostic factors (sex, clinical class, SFJ reflux, diameter, type of device, and length of treated vein), but a validated, prognostic model does not yet exist in practice.[28] At one year follow-up, 10 of our remaining 220 patients (4.5 per cent) had a partial occlusion of the treated GSV with no reflux or only proximal reflux (mGELEV 1 or 2). None of the patients reviewed had a patent, refluxing vein (mGELEV 0). Development of an insufficient anterior accessory saphenous vein (AASV) was noted in four patients in each group at one year follow-up. All eight of these patients had a fully obliterated GSV (mGELEV 6). As existence of reflux in the anterior accessory saphenous vein was an exclusion criterion for this study, the occurrence of the insufficient AASV was certain *de novo*.

Meta-analysis showed no difference in recurrence rate and need for re-intervention five years after treatment when comparing endovenous laser therapy or RFA with surgery. However, it is recommended to conduct more trials assessing long-term outcomes of endovenous techniques.[29]

The improvement in quality of life after vein treatment is a substantial element in evaluating treatment success, as patients experience considerable discomfort from chronic venous disease.

Disease-specific QoL, assessed by CIVIQ-20, was better in both groups after one month compared to preoperative values. R-VCSS scores improved significantly in both groups after one year. There were no significant differences between the treatments regarding r-VCSS or CIVIQ-20 scores.

Although the mean pain score five days after treatment was significantly higher for EVLA than for RFA, the difference of 0.34 was not considered clinically relevant. Also, postoperative use of analgesics, return to daily activities, duration of work incapacity and patient satisfaction were comparable between the two groups. RFA was associated with slightly more postoperative ecchymosis, compared to the use of EVLA.

A systematic review published in 2016 on EVTA of the GSV suggested that EVLA is associated with more postoperative pain than RFA.[30] It should also be mentioned that the studies included in this review used a laser wavelength of 980 nm and bare-tip fibers. Prospective studies using a 1470-nm laser reported lower postoperative pain using EVLA as compared to RFA.[17, 19]

Bozoglan *et al.* compared these two techniques in the same patient, thereby reducing the subject-dependent factor to a minimum. EVLA and RFA had similar success rates (complete occlusion in 100% of saphenous veins (60 patients, both legs) occlusion at 6 months). However, in terms of pain and patient satisfaction, 1470-nm EVLA with RFT was superior to RFA.[23]

Endovascular thermal ablation techniques may result in endothermal heat-induced thrombosis (EHIT), a form of DVT. The actual incidence, clinical significance as well as risk factors remain poorly characterized.[31]The ablation distance peripheral to the deep venous junction was held on 2 cm, prompted by among other a retrospective review showing a trend toward decreased rate of EHIT.[32] The EHIT typically resolves by 2 weeks and always within 7 weeks.

We however performed our first postablation ultrasound at one month postprocedure. Consequently, we can-

not make a statement about observed EHIT. At this first follow-up, ultrasound performers did however not observe thrombi extending further than the SFJ, corresponding to EHIT level 1 by Kabnick.

### Limitations of the study

The limitations of this study should be acknowledged.

Initially this study was designed as a three-center study. Unfortunately, one center failed to send the results of their included patients. The number of included patient in that center was very low so we decided not to include any results of that center. This decision unfortunately resulted in delays later in the course of the study. As a result the study may be under-powered. Consequently, the non-inferiority threshold was changed from less than 5% less than 7.5% difference. This study included 280 which is still more than many other comparative randomized trials.[24, 25]

As mentioned, the physician who evaluated the patients during follow-up visits was the same as the one who treated the patient, and was consequently aware of the technique used.

Third, sixty of the 280 patients did not complete the one-year follow-up. Regarding long-term efficacy of EVTA of the GSV, this study follow-up is limited to twelve months. Future studies could focus on recurrence following EVTA techniques.

## Conclusions

In conclusion, this two-center, prospective trial compared the clinical effectiveness of endovenous laser ablation, using a 1470-nm Tulip-Tip™ fiber and radiofrequency ablation, ClosureFast™ VNUS. Treatment of the GSV resulted in equal occlusion rates at one year of follow-up, with comparable side-effect profiles. No between-group differences in quality of life were shown.

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*Conflicts of interest.*—Marc E. Vuylsteke is the co-inventor of the Tulip-Tip fibre, but has no financial involvement. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

*Funding.*—This research was funded by the Benelux Society of Phlebology (research grant) and the European Venous Forum (EVF Research Grant). The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

*Authors' contributions*.—Anne-Cathérine Kempeneers has given substantial contribution to the conception of the manuscript, analysis and interpretation of the data; Sarah Thomis and Marc E. Vuylsteke have given substantial contributions to the design of the trial; Beate Bechter-Hugl, Sarah Thomis, Daphne van den Bussche and Marc E. Vuylsteke to acquisition of the data; all authors have participated to drafting the manuscript, Anne-Cathérine Kempeneers, Beate Bechter-Hugl and Daphne van den Bussche revised it critically; Mathieu M. Vuylsteke has done statistical analysis. All authors read and approved the final version of the manuscript.

*History.*—Article first published online: February 15, 2022. - Manuscript accepted: February 8, 2022. - Manuscript revised: January 13, 2022. - Manuscript received: July 11, 2021.

*Supplementary data.*—For supplementary materials, please see the HTML version of this article at www.minervamedica.it