Two-year results of a multicenter randomized controlled trial comparing Mechanochemical endovenous Ablation to RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence (MARADONA trial)

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ABSTRACT

Objective: Endothermal techniques have proved to be effective for treatment of incompetent truncal veins. The tumescentless mechanochemical ablation (MOCA) technique has become an alternative treatment modality, but its outcome with regard to endothermal techniques is still unclear.

Methods: A multicenter prospective randomized controlled trial was designed comparing MOCA with radiofrequency ablation (RFA) to treat great saphenous vein incompetence with the hypothesis that MOCA is associated with less postprocedural pain and a comparable anatomic and clinical success rate at 1-year follow-up. Disease-specific quality of life and general health-related quality of life (HRQoL) were measured using questionnaires. Inclusion was terminated prematurely because reimbursement was suspended.

Results: A total of 213 patients (46.3% of intended number of patients) were randomized, of whom 209 were treated (105 in the MOCA group and 104 in the RFA group). Overall median pain scores during the first 14 days were lower after MOCA (0.2 vs 0.5 after RFA; $P = .010$), although the absolute difference was small. At 30 days, similar complication numbers (MOCA, n = 62; RFA, n = 63) and HRQoL scores (Aberdeen Varicose Vein Questionnaire: MOCA, 8.9; RFA, 7.6; $P = .233$) were observed. Hyperpigmentation was reported in seven patients in the MOCA group and two patients in the RFA group ($P = .038$). In the MOCA group, there were four complete failures (3.8%) compared with none in the RFA group ($P = .045$), although in one patient at 1 year, the vein showed occlusion. Median 30-day Venous Clinical Severity Score (VCSS) was significantly lower at 30 days after MOCA (1.0 vs 2.0 in the RFA group; $P = .001$), whereas VCSS was comparable at baseline (MOCA, 4.0; RFA, 5.0; $P = .155$). The 1- and 2-year anatomic success rate was lower after MOCA (83.5% and 80.0%) compared with RFA (94.2% and 88.3%; $P = .025$ and .066), mainly driven by partial recanalizations. After 2 years of follow-up, no differences were observed in the number of complete failures.

Similar clinical success rates at 1 year (MOCA, 88.7%; RFA, 93.2%; $P = .315$) and 2 years (MOCA, 93.0%; RFA, 90.4%; $P = .699$) and no differences in HRQoL scores on the Aberdeen Varicose Vein Questionnaire at 1 year (MOCA, 7.5; RFA, 7.0; $P = .753$) and 2 years (MOCA, 5.0%; RFA, 4.8%; $P = .573$) were observed. There were two cardiac serious adverse events, a ventricular fibrillation in the MOCA group (1 year) and an unstable angina in the RFA group (2 years). One deep venous thrombosis occurred in the RFA group on 1-year duplex ultrasound, without clinical sequelae.

Conclusions: Unilateral treatment with MOCA in the short term resulted in less postoperative pain but more hyperpigmentation compared with RFA and a faster improvement in VCSS. More anatomic failures were reported after MOCA, mostly driven by partial recanalizations, but both techniques were associated with similar clinical outcomes at 1 year and 2 years. (J Vasc Surg: Venous and Lym Dis 2019;7:364-74.)

Keywords: Great saphenous vein incompetence; Radiofrequency ablation; Mechanochemical ablation; Quality of life; Randomized controlled trial

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Chronic venous incompetence may cause substantial functional limitation and has a negative impact on health-related quality of life (HRQoL).[1] The prevalence of chronic venous disease in the adult population has been reported to be as high as 60%, and the incidence of varicose veins ranges from 20% to 64%.[2] Incompetent truncal veins can be treated by endothermal techniques, including endovenous laser ablation and radiofrequency ablation (RFA).[3,4] These techniques result in less hematoma, less pain, superior cosmetics, and earlier resumption of normal activities and work compared with saphenous removal surgery.[5-7] Because of the risk of thermal injury to surrounding tissues, tumescence anesthesia is indicated. Still, postoperative pain that may last >10 days develops in a subset of patients.[5-7] RFA occlusion rates have been reported at >92% after 3 to 5 years of follow-up,[3,8-11] and nerve injury after RFA is rare.[12] Mechanochemical ablation (MOCA), using the ClariVein device (Vascular Insights, Quincy, Mass), was developed as a nonheat-based tumescentless alternative. A rotating wire is used to create vasospasm and vessel wall preparation enabling sclerosant to penetrate into the vessel wall. Recent reviews showed anatomic success rates at 12 months ranging from 87% to 97%.[13-15] Major complications, particularly nerve injury, were rare (≤0.2%).

The aim of this multicenter randomized controlled trial was to evaluate whether MOCA is associated with less postprocedural pain and comparable anatomic and clinical success rates at 1 year compared with RFA in patients with great saphenous vein (GSV) incompetence.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, prospective, randomized trial
- **Key Findings:** At 1 and 2 years, anatomic success rate was lower after mechanochemical ablation (MOCA; 83.5% and 80.0%) compared with radiofrequency ablation (RFA; 94.2% and 88.3%; $P = .025$ and .066) because of partial recanalizations. Similar clinical success rates (MOCA, 88.7% and 93.0%; RFA, 93.2% and 90.4%; $P = .315$ and .699) were observed.
- **Take Home Message:** The study suggests that MOCA is a good alternative for treatment of great saphenous vein incompetence at 2 years of follow-up, although partial recanalization is more frequent than after RFA.

METHODS

Ethics statement

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Medical Ethics Committee of Nijmegen (CMO 2011-091) and the local Institutional Review Board of each participating center. Eligible patients who met the inclusion criteria were fully informed, and those who signed the informed consent were included.

Study design

The design of the study was a multicenter randomized controlled trial comparing MOCA with RFA for GSV incompetence.[16] Four vascular centers in The Netherlands participated. The physician's experience of ≥20 for both techniques was mandatory before initiation to prevent a learning curve bias.

Patients were included when suffering from GSV incompetence (>3 mm and <12 mm), with a clinical class between C2 and C5 (Clinical, Etiology, Anatomy, and Pathophysiology classification).[17] Exclusion criteria were an active ulcer, previous surgery or treatment of the ipsilateral GSV, use of oral anticoagulants, pregnancy or lactation, previous deep venous thrombosis, immobilization, contraindication or known allergy to sclerosant, coagulation disorders or increased risk of thromboembolism, severe renal or liver insufficiency, and severe peripheral artery disease.

Randomization was performed using an online randomization module with block randomization per site. Data were collected using case record forms and stored in a central online database with audit trail (The Research Manager, Deventer, The Netherlands) and monitored. Adverse events and outcomes during the first 30 days were reported to the Data and Safety Monitoring Board and to the Central Committee on Research involving Human Subjects. An interim safety analysis was performed after inclusion of the first 104 patients.

End points

The primary end points were postprocedural pain, evaluated using a 100-point visual analog scale during 2 weeks after treatment, and anatomic success at 1 year. Secondary end points included anatomic success, clinical success using the Venous Clinical Severity Score (VCSS),[18] 30-day morbidity, procedural time, procedural pain, disease-specific quality of life (Aberdeen Varicose Vein Questionnaire [AVVQ]) and general HRQoL (36-Item Short Form Health Survey [SF-36]), time to return to daily activities or work, reintervention rate, and any additional varicose vein treatment during 2 years of follow-up.

Definitions

The full list of definitions has been published previously.[16] Briefly, technical success was the initial success of the procedure (ie, the catheter safely placed at the defined location and the GSV treated without technical problems). Anatomic success was an occlusion of the treated GSV segment, objectified by duplex ultrasound. Failure of treatment is defined as recanalization, which could be complete or partial (>10 cm).[19] Clinical success was defined as an improvement in the VCSS of ≥1 point.[3]

Postprocedural complications were those occurring within 30 days. Major complications included deep venous thrombosis, pulmonary embolism, skin burn, and saphenous neuralgia.

Treatment modalities

MOCA. Patients were treated in the supine position. The incompetent GSV was punctured under ultrasound guidance, and a guidewire was inserted. A 4F introduction sheath was introduced, and the tip of the ClariVein catheter was placed 5 mm below the orifice of the superficial epigastric vein or 2 cm below the saphenofemoral junction. The wire was activated for 10 seconds to induce vasospasm. The device was withdrawn manually with a speed of 7 s/cm while the liquid sclerosant was continuously injected using 2 mL of 3% polidocanol for the first 10 to 15 cm and 1.5% polidocanol for the remainder.[20,21]

RFA. Patients were treated in the supine position. The incompetent GSV was punctured under ultrasound guidance, and a guidewire was inserted. The ClosureFast endovenous RFA catheter (Covidien Commercial Ltd, Watford, United Kingdom) containing a 7-cm-long heating element was positioned at the location described before. Tumescence anesthesia, consisting of 500 mL of 0.9% NaCl including 20 mL of 8.4% sodium bicarbonate and 50 mL of lidocaine 1% with epinephrine 1:200,000, was injected along the entire segment. A volume of 10 mL per centimeter-treated vein was used. Every 20 seconds, a new 7-cm segment of the GSV was treated after pullback. The most proximal segment of the GSV was treated with two cycles as recommended by the manufacturer.

After treatment, the deep venous system and the treated segment were checked using duplex ultrasound. For both techniques, a compression stocking (20-30 mm Hg) was applied continuously for 24 hours and then daily for 2 weeks. Patients were advised to take acetaminophen when necessary and allowed to resume normal activities immediately. No concomitant phlebectomy or sclerotherapy was scheduled to be performed unless indicated by the treating physician.

Clinical follow-up and duplex ultrasound were scheduled at 30 days (±7 days), 1 year (±1 month), and 2 years (±2 months) and included clinical evaluation, duplex ultrasound imaging, and SF-36 and AVVQ scores. Ultrasound assessments were performed by vascular technicians who were blinded for treatment.

Sample size calculation

A sample size calculation was performed for the early end point on the hypothesis that MOCA would have less postprocedural pain during the first 2 weeks. To evaluate a 30% reduction, 58 patients per group were needed (α, 5%; power, 80%). Sample size calculation was also performed on the basis of the assumption that MOCA would have a similar anatomic and clinical success rate at 1 year compared with RFA. For a noninferiority trial with an effect size (anatomic success) of 93% and a margin of 7%, 210 patients per group were needed (α, 5%; power, 80%). Taking into account 10% dropout in each arm, 230 patients needed to be included in each study arm.

Statistical analyses

Normality was tested using the Kolmogorov-Smirnov test. Data were analyzed on an intention-to-treat (ITT) principle using a Student *t*-test (normal distribution) or Mann-Whitney *U* test (skewed distribution). Continuous variables are presented as means and standard deviation or median and interquartile range if applicable. Categorical data are presented as number followed by percentage. Differences between groups were tested with the Kruskal-Wallis test and nominal data by the χ^2 test. Analyses of variance with repeated measures design was used to analyze changes over time in pain scores, VCSS, and AVVQ score. Anatomic and clinical success data were analyzed using Kaplan-Meier analyses including censoring for patients lost to follow-up. Differences between treatment modalities were tested using the log-rank test. In addition, per-protocol analyses were performed. Two-sided *P* value $< .05$ was considered significant. Statistical analyses were performed using SPSS Statistics (version 22.0 for Windows; IBM Corp, Armonk, NY).

RESULTS

Between October 2012 and January 2015, there were 295 eligible patients screened, of whom 82 appeared to be screen failures (Fig 1). A total of 213 patients were randomized (46.3% of intended number of patients). Four withdrew consent after randomization, resulting in 209 treated patients, including 105 in the MOCA group and 104 in the RFA group. Reimbursement of MOCA was suspended and enrollment was stopped at the end of 2014. Because it took ≥1 year for MOCA to be reimbursed again, it was advised by the ethical committee to terminate the study.

Baseline characteristics

Baseline characteristics are shown in Table I. The majority of patients were assigned to class C3 or C4a ($P = .223$) without differences in VCSS, SF-36, and AVVQ scores between groups. The most frequently mentioned symptoms included "legs feeling heavy" (MOCA, 77.4%; RFA, 72.8%; $P = .448$) and ankle edema (MOCA, 75.5%; RFA, 84.5%; $P = .105$). Other symptoms included pain (MOCA, 45.3%; RFA, 53.4%; $P = .241$), nightly cramps (MOCA, 39.6%; RFA, 40.8%; $P = .865$), restless legs (MOCA, 38.7%; RFA, 33.0%; $P = .393$), and itching (MOCA, 27.4%; RFA, 28.2%; $P = .898$). In both groups, one patient had an active ulcer with a diameter <2 cm at baseline (protocol deviations).

In the MOCA group, 21.7% of patients previously underwent varicose vein treatment, mainly sclerotherapy, compared with 27.7% of patients in the RFA group

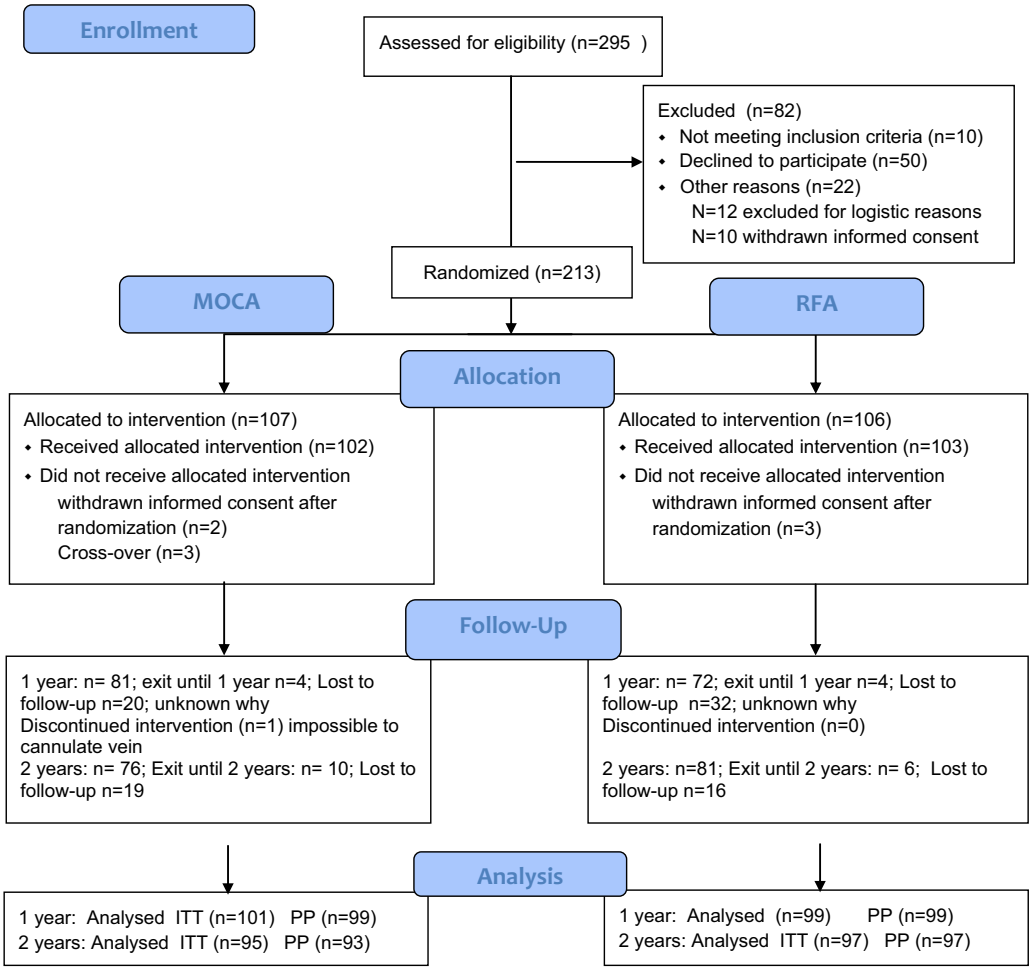

Fig 1. Inclusion flow chart. *ITT,* Intention to treat; *MOCA,* mechanochemical ablation; *PP,* per protocol; *RFA,* radiofrequency ablation.

($P = .095$). A comparable quantity of patients reported pregnancy in the medical history (MOCA, 38.7%; RFA, 31.1%; $P = .249$) and a family history of varicose veins (MOCA, 51.9%; RFA, 61.2%; $P = .176$).

Anatomic and procedural details

The diameter at the saphenofemoral junction was similar in both groups, as was the length of the treated segment (Table I). Technical success was achieved in all but one patient in the MOCA group and all patients in the RFA group. In the only failure, it was impossible to cannulate the GSV. Three crossovers occurred in the MOCA group. In both groups, six patients had adjunctive treatments during the initial procedure. In the MOCA group, 3 had additional foam treatment and 1 phlebectomy of ipsilateral side branches, 1 had sclerotherapy in the contralateral leg, and another patient had a crossectomy for an insufficient anterior accessory saphenous vein. In the RFA group, 4 patients had foam treatment for side branches, 2 had additional RFA on the contralateral GSV, and 1 had additional RFA of a large side branch. Median procedural pain score was similar (3; range, 1-5), as was the procedural time (MOCA, 12.0 minutes [range, 5.0-45.0 minutes]; RFA, 13.0 minutes [range, 4.0-85.0 minutes]).

Early outcomes

Overall, the complication rate was similar without procedure-related serious adverse events (Table II), but hyperpigmentation occurred more often in the MOCA group. Overall median pain scores during the first 14 days were lower after MOCA ($P = .010$; Table III). MOCA-treated patients had less pain on every postprocedural day, reaching significance on days 5, 6, 8, and 9 (Fig 2). The use of pain medication was similar, and there were no differences between groups in return to daily activities or work, if applicable. In the RFA group, four patients underwent additional treatments between procedure and 4 weeks of follow-up; two reported ipsilateral sclerotherapy, one sclerotherapy of both legs, and another contralateral RFA combined with sclerotherapy.

Anatomic and clinical outcomes. Follow-up compliance for the 30-day visit was similar (MOCA, 97.2%; RFA, 100%). In the MOCA group, four anatomic failures were

Table I. Baseline and procedural characteristics stratified by treatment

	MOCA (n = 105)	RFA (n = 104)
Age, years	54.9 (16.3-81.2)	53.4 (22.8-77.9)
Female	62.4	59.3
Height, cm	172 (154-196)	173 (156-195)
Weight, kg	80 (55-140)	80 (50-110)
Duration of symptoms	24.0 (2.0-720)	24.0 (1.0-204)
Clinical class (CEAP)		
C2	5.9	4.2
C3	59.8	66.7
C4a	31.4	22.9
C4b	0	3.1
C5	2.0	3.1
Individual components of the VCSS[a]		
Pain	7.5	6.8
Varicosis	7.5	8.7
Ankle edema	13.2	15.5
Skin pigmentation	0.9	2.9
Inflammation	0	0
Induration	0	1.9
No. of active ulcers	0.9	0.9
Size of ulcers	0	0
Duration of ulcers	1	0
Compression therapy	4.7	3.9
Diameter of GSV at SFJ junction, mm	6.0 (0.8-12.0)	6.0 (1.2-14.0)
Length of treated segment, mm	45.0 (15.0-65.0)	45.0 (15.0-57.0)
Duration of procedure, minutes	12.0 (5.0-45.0)	13.0 (4.0-85.0)
Used dosage		
1.5%	6.0 (1.0-10.0)	
3.0%	2.0 (1.0-7.0)	
Amount of cycles	6 (4-10)[b]	7 (2-14)
Immediate partial failure (DUS)	1 (0.9)	1 (1.0)

CEAP, Clinical, Etiology, Anatomy, and Pathophysiology; *DUS*, duplex ultrasound; *GSV*, great saphenous vein; *MOCA*, mechanochemical ablation; *RFA*, radiofrequency ablation; *SFJ*, saphenofemoral junction; *VCSS*, Venous Clinical Severity Score.
Categorical variables are presented as percentage. Continuous variables are presented as median (interquartile range).
[a]The percentage of patients who scored the worst category are presented.
[b]In patients randomized for MOCA but treated with RFA.

Table II. Overview of the complications until 30 days of follow-up

	MOCA	RFA	*P* value
Total No. of complications	62	63	.257
No. of patients with ≥1 complication	35 (34.0%)	42 (40.8%)	.339
Superficial thrombophlebitis	12	8	.129
Induration	17	12	.071
Wound infection puncture site	0	2	.191
Saphenous neuralgia	1	3	.399
Pain >1 week	10	17	.276
Hematoma	14	15	.699
Skin burn	0	0	–
Hyperpigmentation	7	2	.038
Other	0	3	
Swelling and fever		1	
Ulcur reopened		1	
Blister at plaster site		1	

MOCA, Mechanochemical ablation; *RFA*, radiofrequency ablation.

found, three complete and one partial recanalization (Table III). Two of these patients reported an improved VCSS and the other a worsened VCSS compared with baseline (one patient was lost to follow-up). Two of them were re-treated with RFA within 1 year, and the other, having a partial recanalization, showed a completely occluded GSV at 1 year without reintervention. In the RFA group, 30-day anatomic success was 100% ($P = .045$). The MOCA group showed a significantly lower VCSS compared with the RFA group ($P = .001$; Fig 3). The incidence of ankle edema was significantly lower after MOCA, with a similar incidence at baseline ($P = .002$).

Quality of life. Compliance on the questionnaires was 91.3% and 85.4% in the MOCA and RFA groups, respectively ($P = .193$). No differences were observed in the number of drawn blocks and total AVVQ score (Fig 4). Both groups had similar SF-36 scores, except for energy/fatigue, which was slightly higher in the RFA group (Fig 5).

Outcomes at 1 and 2 years

Anatomic and clinical outcomes. Follow-up compliance was 86.8% and 72.4% in the MOCA group and 82.7% and 78.6% in the RFA group at 1 year and 2 years, respectively (Table IV). The 1- and 2-year anatomic success rate was lower after MOCA (83.5% and 80.0%) compared with RFA (94.2% and 88.3%; $P = .025$ and .066), mainly driven by partial recanalizations. There were nine complete recanalizations in the MOCA group and four complete recanalizations in the RFA group until 1 year ($P = .163$) and nine and seven complete failures, respectively, until 2 years of follow-up ($P = .631$). In the majority of cases, recanalization occurred at the proximal segment. There was no difference between groups in length of recanalization (MOCA, 15 cm [range, 10-20 cm]; RFA, 18 cm [range, 13.5-28.0 cm]) and percentage recanalization of the treated segment (MOCA, 33.3% [range, 32.8%-50.0%]; RFA, 50.0% [range, 32.7%-66.7%]).

Absolute VCSSs were similar in both arms at 1 year and 2 years (Fig 3) with a comparable improvement compared with baseline (Fig 6). Clinical success was

Table III. Early outcomes stratified by treatment

	MOCA	RFA	*P* value
First 14 days	(n = 103)	(n = 103)	
Pain score			
Median (range)	0.2 (0.0-0.8)	0.5 (0.2-1.3)	.010
Mean	0.686	0.998	
Restart of daily activities, days			
Median (range)	1.0 (0.0-1.0)	1.0 (1.0-2.0)	.085
Mean	1	1.43	
Range	0-6	0-6	
Restart of work (if applicable), days			
Median (range)	1.0 (1.0-3.0)	2.0 (1.0-4.0)	.129
Mean	2.28	2.98	
Range	0-13	0-15	
30-day outcomes	(n = 103)	(n = 103)	
Partial failure	5 (4.9%)	1 (1.0%)	.100
Complete failure	4 (3.8%)[a]	0	.045
Individual components of the VCSS[b]			
Pain	1	0	.519
Varicosis	1	1	.531
Ankle edema	0	10.7	.002
Skin pigmentation	0	1	.520
Inflammation	1	0	.220
Induration	0	0	.521
No. of active ulcers	0	1	.316
Size of ulcers	0	0	.314
Duration of ulcers	0	1	.316
Compression therapy	1	1	.168
Patient satisfaction score	9.0 (8-9)	8.0 (8-9)	.077

MOCA, Mechanochemical ablation; *RFA*, radiofrequency ablation; *VCSS*, Venous Clinical Severity Score.
[a]One patient with failure at 4 weeks showed occluded great saphenous vein at 1-year follow-up.
[b]The percentage of patients who scored the worst category is presented.

similar in both arms at 1 year (MOCA, 88.7%; RFA, 93.2%; $P = .315$) and 2 years (MOCA, 93.0%; RFA, 90.4%).

Through 2 years of follow-up, three reinterventions were performed in the MOCA group vs two in the RFA group ($P = .675$). However, one reintervention in the MOCA group and four reinterventions in the RFA group were scheduled. There were two cardiac serious adverse events reported; in the MOCA group, a patient was hospitalized for ventricular fibrillation and was treated with cardioversion. In the RFA group, a patient was hospitalized for unstable angina and had a coronary bypass procedure. One new deep venous thrombosis was reported in a patient treated with RFA on 1-year duplex ultrasound examination, but without clinical sequelae.

Quality of life. Compliance on the questionnaires at 1- and 2-year follow-up was 93.8% and 81.1% in the MOCA group and 95.8% and 79.4% in the RFA group, respectively (NS). No differences were observed between groups in drawn blocks and total AVVQ scores at 1- and 2-year follow-up (Fig 4). Both groups scored similarly on all domains of the SF-36 (Fig 5). Compared with baseline, patients treated with MOCA showed a significant improvement at 1 year in physical and social functioning, both physical and emotional role functioning, mental health, and pain. Patients treated with RFA showed only an improved physical functioning and pain score at 1 year compared with baseline. Two years after treatment in the MOCA group, physical functioning, physical role functioning, pain, and general health perception remained improved compared with baseline, whereas in the RFA group, only pain and general health perception remained improved and health change deteriorated.

DISCUSSION

This study showed that MOCA of the GSV results in less postoperative pain, although the absolute difference is small. Clinical success rates were equal to those of RFA

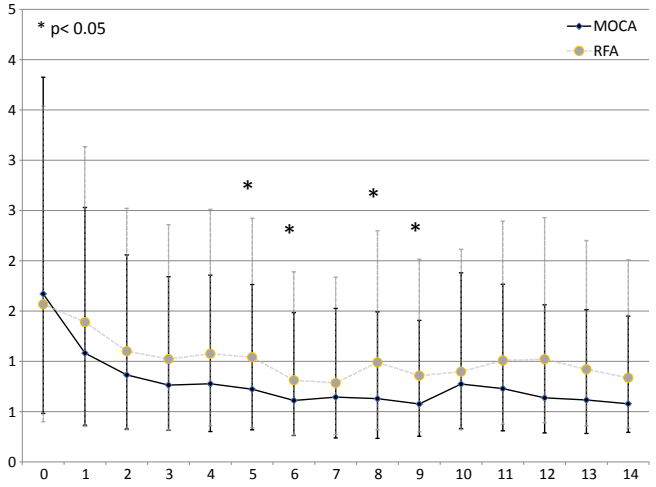

Fig 2. Pain scores during the first 14 days, including procedure day for both treatment groups (mean and 95% confidence intervals). *$P < .05$ between treatments at that day. *MOCA,* Mechanochemical ablation; *RFA,* radiofrequency ablation.

at 1- and 2-year follow-up, but with more anatomic failures, especially partial recanalizations.

The lower pain scores for MOCA are in line with previous data from a prospective registry.[21] MOCA was related to a better clinical outcome at 30 days, mainly driven by less edema. Given the equal incidence of induration and hematoma, this difference is not likely to be caused by heat-related complications. Another potential explanation could be that liquid sclerosant diffuses into side branches that are subsequently occluded and as such treated instantly. At 1-year follow-up, differences between groups disappeared, with a significant improvement in clinical outcomes for both groups.

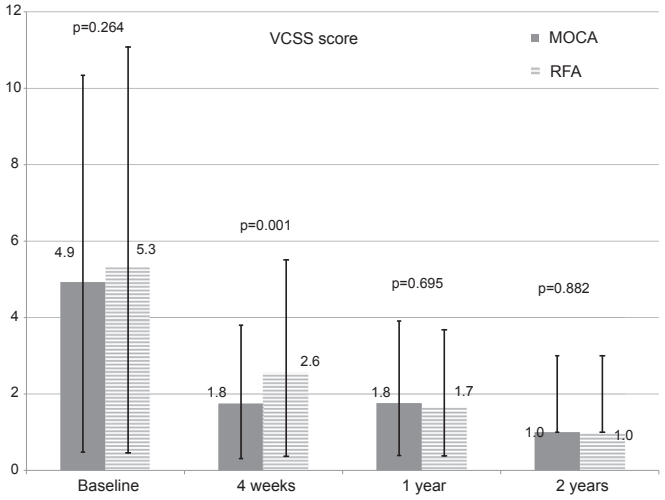

Fig 3. Venous Clinical Severity Score (*VCSS*) for both treatment groups at baseline, 4 weeks, 1 year, and 2 years of follow-up. *MOCA,* Mechanochemical ablation; *RFA,* radiofrequency ablation.

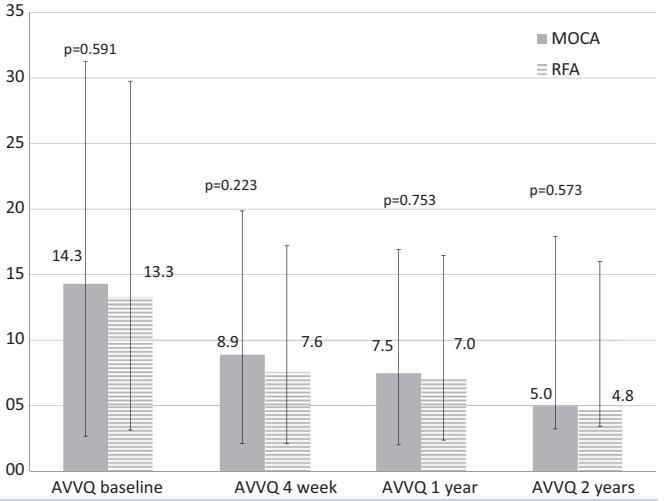

Fig 4. Changes in Aberdeen Varicose Vein Questionnaire (*AVVQ*) scores over time for both treatment groups. *MOCA,* Mechanochemical ablation; *RFA,* radiofrequency ablation.

Equal clinical outcome was also reported at 6-month follow-up in another trial.[22] The main difference with this study is that more concomitant avulsions were performed in that trial, in 74% of MOCA- and 68% of RFA-treated patients. A recent report of the Vascular Quality Initiative Varicose Vein Registry described similar incidence of adjunctive procedures (76%).[23] In this study, the number of concomitant and adjunctive treatments is low, which was also the case in our previously published case series.[16,24] This is due to a different treatment algorithm in The Netherlands, where treatment effect is awaited before concomitant procedures are performed. Because of the elimination of GSV reflux, branch varicosities may diminish in size or resolve completely in time.[25] RFA with concomitant phlebectomy may increase the risk of endovenous heat-induced thrombosis.[26]

This study showed significantly more anatomic failures at 1 year and 2 years after MOCA compared with RFA, of which a large proportion was partial. Whether the partial recanalizations will be progressive in time and lead to clinical symptoms remains to be seen. Future reinterventions are scheduled, one in the MOCA group and four in the RFA group. Prolonged follow-up of these cohorts is therefore crucial, particularly because a further decline may be expected on the basis of an earlier cohort study.[24] The anatomic success rate of MOCA might have been affected by the chosen sclerosant. Polidocanol is the only available option in The Netherlands to date, whereas in most studies, sodium tetradecyl sulfate (Sotradecol) was used. Sotradecol is related to more endothelial cell loss and damage to the media compared with polidocanol.[27] The use of a higher concentration of polidocanol was not feasible, given the maximum dose that can be applied.[16] At present, the treatment protocol has already been changed, with the

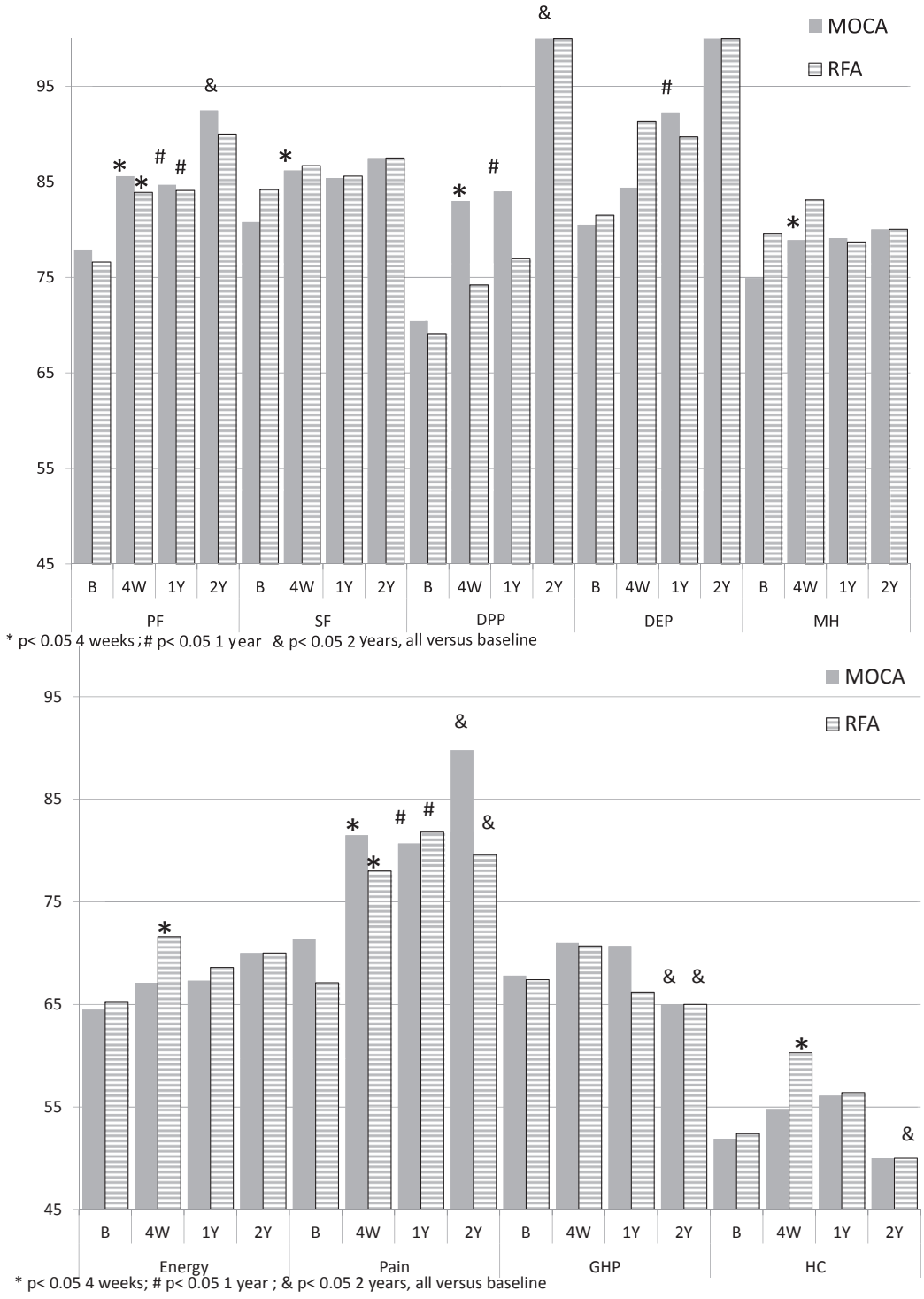

Fig 5. Changes in 36-Item Short Form Health Survey (SF-36) scores over time for both treatment groups. *B,* Baseline; *DEP,* role functioning/emotional; *DPP,* role functioning/physical; *GHP,* general health perception; *HC,* health change; *MH,* mental health; *MOCA,* mechanochemical ablation; *PF,* physical functioning; *RFA,* radiofrequency ablation; *SF,* social functioning; *4W,* 4-week follow-up; *1Y,* 1-year follow-up; *2Y,* 2-year follow-up. $^{*}P < .05$ for changes after 4 weeks compared with baseline. $^{\#}P < .05$ for changes after 1 year compared with baseline. $^{\&}P < .05$ for changes after 2 years compared with baseline.

Table IV. The 1- and 2-year outcomes stratified by treatment

	MOCA	RFA	*P* value
1-year outcomes	(n = 81)	(n = 72)	
Anatomic failures at 1-year follow-up	15 (16.5)	5 (5.8)	.025
Complete failures	8 (8.8)	3 (3.5)	.144
Complete failures until 1 year (including early)	9 (8.6)	4 (3.9)	.163
Median improvement in VCSS compared with baseline	3 (2-4)	4 (2-5)	.170
Individual components of the VCSS[a]			
Pain	0	0	.995
Varicosis	0	0	.160
Ankle edema	0	5.6	.221
Skin pigmentation	0	0	.590
Inflammation	0	0	.368
Induration	0	0	.378
No. of active ulcers	0	0	NA
Size of ulcers	0	0	NA
Duration of ulcers	0	0	NA
Compression therapy	1.2	1.4	.720
Reintervention (all RFA)	2 (2.2)	1 (1.1)	.587
2-year outcomes	(n = 76)	(n = 81)	
Anatomic failures at 2-year follow-up	21 (20.0)	12 (11.7)	.066
Complete failures	6 (8.2)	5 (6.5)	.703
Complete failure until 2 years	9 (8.6)	7 (6.8)	.631
Time to fail, months	12.8 (10.0-13.7)	15.8 (11.9-24.1)	.107
Improvement in VCSS compared with baseline	3 (2-5)	4 (3-5)	.050
Individual components of the VCSS[a]			
Pain	0	1.0	.256
Varicosis	0	1.0	.196
Ankle edema	0	2.9	.370
Skin pigmentation	0	0	.589
Inflammation	0	0	.325
Induration	0	0	NA
No. of active ulcers	0	0	NA
Size of ulcers	0	0	NA
Duration of ulcers	0	0	NA
Compression therapy	1	1.9	.815
Reintervention between 1 and 2 years	1 (1.3)	1 (1.3)	.978
Reintervention until 2-year follow-up	3 (2.9)	2 (2.0)	.675
Future reintervention scheduled	1 (1.4)	4 (5.1)	.192
Exit until 2 years	4 (4.7)	2 (2.3)	.538

MOCA, Mechanochemical ablation; *NA*, not applicable; *RFA*, radiofrequency ablation; *VCSS*, Venous Clinical Severity Score.
Categorical variables are presented as number (%). Continuous variables are presented as median (interquartile range).
[a]The percentage of patients who scored the worst category are presented.

proximal part treated twice when it is not fully collapsed after the first cycle. An experimental study underlined the hypothesis that mechanical manipulation increases effectiveness by inducing endothelial damage and probably vasoconstriction.[28] Repeated treatment of the proximal segment might therefore reduce the failure rate. To evaluate possible bias, we performed per-protocol analyses and analyses of the data of Rijnstate only. No different results were found compared with the results described (data not shown).

Evidence has been accumulating on the effectiveness of MOCA, showing anatomic success rates of 87% to 92%.[13-15] However, there is clear heterogeneity in study protocols with respect to pullback rates and concentrations, volumes, and type of sclerosant used, which may affect the anatomic success rate. Comparative trials

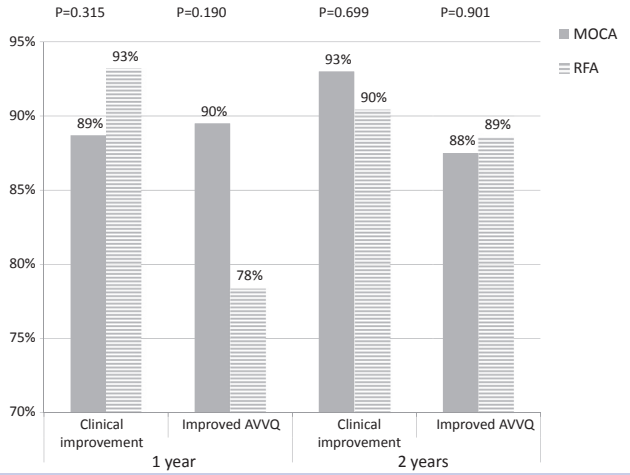

Fig 6. Percentage of patients showing clinical improvement at 1- and 2-year follow-up compared with baseline. *AVVQ,* Aberdeen Varicose Vein Questionnaire; *MOCA,* mechanochemical ablation; *RFA,* radiofrequency ablation.

between MOCA and other nonthermal ablation techniques, such as VenaSeal (Sapheon, Inc, Morrisville, NC) and Varithena (BTG International Ltd, West Conshohocken, Pa), have not been published to date. The 1-year anatomic success rates of these nonthermal techniques are between 90%[29] and 97%.[30] The Laser Ablation vs Mechanochemical Ablation (LAMA) trial, comparing endovenous laser ablation vs ClariVein, is currently being performed and results are awaited.[31]

In comparison to other trials, the number of patients with C2 varicose veins was small. This was related to the policy of the Dutch insurance companies not to reimburse any treatment classified as <C3 during part of the inclusion period. Obviously, this has shifted our study groups into more severe types of venous insufficiency. In addition, reimbursement of MOCA was stopped in early 2015, and as a consequence, the enrollment in this trial was preliminarily ended after consultation of the ethical board. The sample size for the postoperative pain score had already been reached at that point. Our results on anatomic outcome should be interpreted with care as the study is underpowered on this end point.

Evidence of the impact of varicose vein treatment on HRQoL in addition to anatomic success is less robust. Argyriou et al[32] recently reported no difference in HRQoL in comparing different venous interventions, including RFA, with surgical stripping. Midterm outcomes (up to 3 years of follow-up) of MOCA showed that AVVQ and SF-36 scores were improved at all time intervals compared with baseline, which was also observed in this study. Between 12 and 36 months, however, a significant deterioration was observed in VCSS, accompanied by worsening of disease-specific and general quality of life.[24]

This study has limitations. Importantly, the inclusion was terminated before reaching the sample size on anatomic success. Although follow-up compliance was high, not all questionnaires were complete. Establishing high compliance in venous trials is challenging because once patients are cured, the urgency for surveillance is gone. To overcome this, evening and weekend hours for follow-up visits were offered. Finally, groups of failures were too small for robust analyses of predictors of failure. We are aware that these groups do not reflect all patients in real-world practice because of inclusion and exclusion criteria, as occurs in most studies. This is partly due to the fact that using MOCA, bilateral treatment is many times not possible because of the maximum amount of sclerosant that can be used safely at one session.

CONCLUSIONS

In this study, unilateral treatment with MOCA resulted in more hyperpigmentation but less postoperative pain compared with RFA and a faster improvement in VCSS. More anatomic failures were reported after MOCA, mostly driven by partial recanalizations, but both techniques were associated with similar clinical outcomes at 1 year and 2 years.

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AUTHOR CONTRIBUTIONS

Conception and design: RE, MR
Analysis and interpretation: SH, RE, AV, JV, MR
Data collection: SH, AV, JV
Writing the article: SH, MR
Critical revision of the article: SH, RE, AV, JV, MR
Final approval of the article: SH, RE, AV, JV, MR
Statistical analysis: SH
Obtained funding: MR
Overall responsibility: MR

REFERENCES

1. Mallick R, Lal BK, Daugherty C. Relationship between patient-reported symptoms, limitations in daily activities, and psychological impact in varicose veins. J Vasc Surg Venous Lymphat Disord 2017;5:224-37.
2. Wittens C, Davies AH, Baekgaard N, Broholm R, Cavezzi A, Chastanet S, et al. Editor's choice—management of chronic venous disease: clinical practice guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2015;49:678-737.
3. Khilnani NM, Grassi CJ, Kundu S, D'Agostino HR, Khan AA, McGraw JK, et al. Multi-society consensus quality improvement guidelines for the treatment of lower-extremity superficial venous insufficiency with endovenous thermal ablation from the Society of Interventional Radiology, Cardiovascular Interventional Radiological Society of Europe, American College of Phlebology and Canadian Interventional Radiology Association. J Vasc Interv Radiol 2010;21:14-31.

4. van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: a meta-analysis. J Vasc Surg 2009;49:230-9.
5. Brittenden J, Cotton SC, Elders A, Ramsay CR, Norrie J, Burr J, et al. A randomized trial comparing treatments for varicose veins. N Engl J Med 2014;371:1218-27.
6. Shepherd AC, Gohel MS, Brown LC, Metcalfe MJ, Hamish M, Davies AH. Randomized clinical trial of VNUS ClosureFAST radiofrequency ablation versus laser for varicose veins. Br J Surg 2010;97:810-8.
7. Shepherd AC, Gohel MS, Lim CS, Hamish M, Davies AH. Pain following 980-nm endovenous laser ablation and segmental radiofrequency ablation for varicose veins: a prospective observational study. Vasc Endovascular Surg 2010;44:212-6.
8. Proebstle TM, Alm BJ, Gockeritz O, Wenzel C, Noppeney T, Lebard C, et al. Five-year results from the prospective European multicentre cohort study on radiofrequency segmental thermal ablation for incompetent great saphenous veins. Br J Surg 2015;102:212-8.
9. Proebstle TM, Alm J, Gockeritz O, Wenzel C, Noppeney T, Lebard C, et al. Three-year European follow-up of endovenous radiofrequency-powered segmental thermal ablation of the great saphenous vein with or without treatment of calf varicosities. J Vasc Surg 2011;54:146-52.
10. Whiteley MS, Shiangoli I, Dos Santos SJ, Dabbs EB, Fernandez-Hart TJ, Holdstock JM. Fifteen year results of radiofrequency ablation, using VNUS Closure, for the abolition of truncal venous reflux in patients with varicose veins. Eur J Vasc Endovasc Surg 2017;54:357-62.
11. Lawson JA, Gauw SA, van Vlijmen CJ, Pronk P, Gaastra MT, Tangelder MJ, et al. Prospective comparative cohort study evaluating incompetent great saphenous vein closure using radiofrequency-powered segmental ablation or 1470-nm endovenous laser ablation with radial-tip fibers (Varico 2 study). J Vasc Surg Venous Lymphat Disord 2018;6:31-40.
12. Hamann SA, Giang J, De Maeseneer MG, Nijsten TE, van den Bos RR. Editor's choice—five year results of great saphenous vein treatment: a meta-analysis. Eur J Vasc Endovasc Surg 2017;54:760-70.
13. Kugler NW, Brown KR. An update on the currently available nonthermal ablative options in the management of superficial venous disease. J Vasc Surg Venous Lymphat Disord 2017;5:422-9.
14. Sun JJ, Chowdhury MM, Sadat U, Hayes PD, Tang TY. Mechanochemical ablation for treatment of truncal venous insufficiency: a review of the current literature. J Vasc Interv Radiol 2017;28:1422-31.
15. Witte ME, Zeebregts CJ, de Borst GJ, Reijnen M, Boersma D. Mechanochemical endovenous ablation of saphenous veins using the ClariVein: a systematic review. Phlebology 2017;32:649-57.
16. van Eekeren RR, Boersma D, Holewijn S, Vahl A, de Vries JP, Zeebregts CJ, et al. Mechanochemical endovenous Ablation versus RADiOfrequeNcy Ablation in the treatment of primary great saphenous vein incompetence (MARADONA): study protocol for a randomized controlled trial. Trials 2014;15:121.
17. Kistner RL, Eklof B, Masuda EM. Diagnosis of chronic venous disease of the lower extremities: the "CEAP" classification. Mayo Clin Proc 1996;71:338-45.
18. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000;31:1307-12.
19. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011;98:1079-87.
20. van Eekeren RR, Boersma D, Elias S, Holewijn S, Werson DA, de Vries JP, et al. Endovenous mechanochemical ablation of great saphenous vein incompetence using the ClariVein device: a safety study. J Endovasc Ther 2011;18:328-34.
21. van Eekeren RR, Boersma D, Konijn V, de Vries JP, Reijnen MM. Postoperative pain and early quality of life after radiofrequency ablation and mechanochemical endovenous ablation of incompetent great saphenous veins. J Vasc Surg 2013;57:445-50.
22. Lane T, Bootun R, Dharmarajah B, Lim CS, Najem M, Renton S, et al. A multi-centre randomised controlled trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins—final results of the Venefit versus Clarivein for varicose veins trial. Phlebology 2017;32:89-98.
23. Obi AT, Sutzko DC, Almeida JI, Kabnick L, Cronenwett JL, Osborne NH, et al. First 10-month results of the Vascular Quality Initiative Varicose Vein Registry. J Vasc Surg Venous Lymphat Disord 2017;5:312-20.e2.
24. Witte ME, Holewijn S, van Eekeren RR, de Vries JP, Zeebregts CJ, Reijnen MM. Midterm outcome of mechanochemical endovenous ablation for the treatment of great saphenous vein insufficiency. J Endovasc Ther 2017;24:149-55.
25. Monahan DL. Can phlebectomy be deferred in the treatment of varicose veins? J Vasc Surg 2005;42:1145-9.
26. Hicks CW, DiBrito SR, Magruder JT, Weaver ML, Barenski C, Heller JA. Radiofrequency ablation with concomitant stab phlebectomy increases risk of endovenous heat-induced thrombosis. J Vasc Surg Venous Lymphat Disord 2017;5:200-9.
27. McAree B, Ikponmwosa A, Brockbank K, Abbott C, Homer-Vanniasinkam S, Gough MJ. Comparative stability of sodium tetradecyl sulphate (STD) and polidocanol foam: impact on vein damage in an in-vitro model. Eur J Vasc Endovasc Surg 2012;43:721-5.
28. Boersma D, van Haelst ST, van Eekeren RR, Vink A, Reijnen MM, de Vries JP, et al. Macroscopic and histologic analysis of vessel wall reaction after mechanochemical endovenous ablation using the ClariVein OC device in an animal model. Eur J Vasc Endovasc Surg 2017;53:290-8.
29. Morrison N, Gibson K, Vasquez M, Weiss R, Cher D, Madsen M, et al. VeClose trial 12-month outcomes of cyanoacrylate closure versus radiofrequency ablation for incompetent great saphenous veins. J Vasc Surg Venous Lymphat Disord 2017;5:321-30.
30. Gibson K, Kabnick L; Varithena 013 Investigator Group. A multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of Varithena (polidocanol endovenous microfoam 1%) for symptomatic, visible varicose veins with saphenofemoral junction incompetence. Phlebology 2017;32:185-93.
31. Leung CC, Carradice D, Wallace T, Chetter IC. Endovenous laser ablation versus mechanochemical ablation with ClariVein in the management of superficial venous insufficiency (LAMA trial): study protocol for a randomised controlled trial. Trials 2016;17:421.
32. Argyriou C, Papasideris C, Antoniou GA, Georgakarakos E, Papanas N, Lazarides MK, et al. The effectiveness of various interventions versus standard stripping in patients with varicose veins in terms of quality of life. Phlebology 2018;33:439-50.

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