A systematic review and meta-analysis of two novel techniques of nonthermal endovenous ablation of the great saphenous vein

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ABSTRACT

Background: Endothermal treatment of the great saphenous vein (GSV) has become the first-line treatment for superficial venous reflux. Nonthermal ablation has potential benefits for acceptability by patients and decreased risk of nerve injury. We performed a systematic review and meta-analysis to evaluate the efficacy of mechanochemical endovenous ablation (MOCA) and cyanoacrylate vein ablation (CAVA) for GSV incompetence.

Methods: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health Literature, and Cochrane databases were searched for papers published between January 1966 and December 2016. Eligible articles were prospective studies that included patients treated for GSV incompetence and described the primary outcome. Exclusion criteria were full text not available, case reports, retrospective studies, small series ($n < 10$), reviews, abstracts, animal studies, studies of small saphenous vein incompetence, and recurrent GSV incompetence. Primary outcome was anatomic success. Secondary outcomes were initial technical success, Venous Clinical Severity Score, Aberdeen Varicose Vein Questionnaire score, and complications.

Results: Fifteen articles met the inclusion criteria. Pooled anatomic success for MOCA and CAVA was 94.7% and 94.8% at 6 months and 94.1% and 89.0% at 1 year, respectively. Venous Clinical Severity Score and Aberdeen Varicose Vein Questionnaire score significantly improved after treatment with MOCA and CAVA.

Conclusions: These results are promising for these novel techniques that could serve as alternatives for thermal ablation techniques. However, to determine their exact role in clinical practice, high-quality randomized controlled trials comparing these novel modalities with well-established techniques are required. (J Vasc Surg: Venous and Lym Dis 2017;■:1-17.)

Chronic venous incompetence of the lower limbs, which is most commonly caused by incompetence of the great saphenous vein (GSV), is a common disorder. The prevalence of superficial vein reflux is up to 30% in the adult population and increases linearly with age.[1] Chronic venous incompetence has been associated with decreased general and disease-specific quality of life.[2-4]

Endothermal ablation (ETA) treatment of the GSV has become the first-line treatment for superficial venous reflux. ETA has the advantage of avoiding general anesthesia, and a shorter operative time and decreased postoperative pain and morbidity compared with open surgery have been reported.[5-8] The use of ETA has risks; thermal damage to superficial nerves is a known complication.[9] Furthermore, patients undergoing ETA are currently advised to wear compression stockings for at least 1 week after the procedure to reduce pain and to improve physical function.[10]

Newer treatments, especially nonthermal ablation (NTA), have potential benefits for acceptability by patients and also for decreased risk of nerve injury. Three NTA options are currently widely discussed. Ultrasound-guided foam sclerotherapy (UGFS) has been used for a long time and avoids the risk of nerve injury. However, UGFS is not as efficacious as ETA, and studies have reported variable success rates. Davies et al[11] concluded in their literature review in 2016 that anatomic success appeared higher with ETA than with UGFS. Short-term clinical success and patient-reported outcome measures were comparable. There is also a rare but well-documented risk of stroke.[12]

More recently, two NTA alternatives have emerged. The first is mechanochemical endovenous ablation (MOCA), which combines mechanical endothelial damage using a rotating wire with the infusion of a liquid sclerosant (ClariVein; Vascular Insights, Quincy, Mass). The second alternative consists of endovenous delivery of cyanoacrylate tissue adhesive to the vein (cyanoacrylate vein ablation [CAVA]), causing fibrosis (Sapheon VenaSeal Closure [Medtronic, Santa Rosa, Calif] or VariClose [Biolas, Ankara, Turkey]). We performed a systematic review and

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meta-analysis to evaluate the reported efficacy of these two novel NTA methods, MOCA (ClariVein) and CAVA (VenaSeal or VariClose), for GSV incompetence.

METHODS

This report was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews and meta-analyses.[13]

Literature search. Two authors (C.G.V., C.U.) independently searched the literature to identify studies comparing different NTA techniques for GSV incompetence. MEDLINE, Embase, and Cumulative Index to Nursing and Allied Health Literature databases and the Cochrane Database of Systematic Reviews were searched for papers published between January 1966 and December 2016, using the following keywords: "GSV incompetence," "nonthermal ablation," "mechanochemical endovenous ablation," and "cyanoacrylate vein ablation." Free text words were also used instead of Medical Subject Headings to avoid missing recent publications that were not yet given Medical Subject Headings. The "related articles" function in PubMed and reference lists of retrieved articles were also used to identify articles not found in the original search. The search was not restricted to any language. No unpublished data or abstracts were included. A full search strategy is available at request.

Validity assessment. After duplicates were removed, two authors (C.G.V., C.U.) screened the titles and abstracts of the identified studies for relevance. Full texts were obtained of the remaining relevant studies, and two authors (C.G.V., C.U.) read the full-text papers and made a final selection of relevant studies. Two authors (C.G.V., C.U.) independently assessed the methodologic quality of the articles using the Methodological Index for Non-Randomized Studies (MINORS) score, with a global ideal score of 16 for noncomparative studies and 24 for comparative studies.[14] The MINORS score was reported as a percentage of the global ideal score. For this review, a score of ≤8 was considered poor quality, 9 to 14 moderate quality, and 15 to 16 good quality for noncomparative studies. Cutoff points were ≤14, 15 to 22, and 23 to 24, respectively, for comparative studies. Discrepancies between the authors during the search, selection, and quality assessment were resolved by discussion. If agreement was not reached, a third author (M.A.S.) was consulted.

INCLUSION AND EXCLUSION CRITERIA

Studies. All prospective studies that included patients treated for GSV incompetence and described the primary outcome were eligible for inclusion in this review. Exclusion criteria were full text not available, case reports, retrospective studies, small series ($n < 10$), reviews, abstracts, animal studies, studies of short saphenous vein incompetence, and recurrent GSV incompetence. A minimum follow-up of 6 months with duplex ultrasound (DUS) imaging was required for inclusion. Finally, the same criteria were used to screen all cross-references for potentially relevant studies not identified by the initial literature search.

Participants. Studies reported outcomes of patients with GSV incompetence (GSV reflux >500 milliseconds) that was treated by MOCA or CAVA.

Outcome measures. The primary outcome was anatomic success, defined as closure and absence of reflux on DUS imaging in the treated segment of the GSV with a minimum follow-up of 6 months. All of the included studies used DUS imaging to evaluate patients. Secondary outcomes were initial technical success, defined as successful completion of the procedure with occlusion of the GSV on DUS imaging; Venous Clinical Severity Score (VCSS); Aberdeen Varicose Vein Questionnaire (AVVQ) score; and complications.

Data analysis. Two independent authors (C.G.V., C.U.) performed data extraction. Extracted data included study design, sample size, age, sex, comorbidities, diagnostic procedures, type of venous ablation technique, outcome measures as described before, and follow-up duration. Discrepancies were solved by discussion, and a third author (M.A.S.) was consulted in case of disagreement. MetaAnalysist software version 3.1 (Biostat, Englewood, NJ) was used for the meta-analysis. Rates were pooled using a random-effects model. We determined the presence of heterogeneity between the studies by using a forest plot and by performing a χ^2 heterogeneity test. The I^2 index was also calculated. Data are reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate.

RESULTS

Description of studies. The search identified 242 studies. After duplicates were removed and the titles and abstracts were screened for relevance, 25 full-text papers were assessed for eligibility. After the inclusion and exclusion criteria were applied, 15 papers were finally included in this systematic review.[15-29] Of the included papers, seven were on MOCA and eight on CAVA. A flow chart of the complete selection procedure is shown in Fig 1. We excluded 10 studies because of study design (review; $n = 2$), and 8 studies did not report relevant outcome measures.[30-39]

The included studies described 1645 patients. Seven studies reported MOCA outcomes in 691 patients and eight studies reported CAVA outcomes in 954 patients. The cohorts described by Kim et al,[17] Bishawi et al,[15] van Eekeren et al,[20] and Witte et al[21] and the studies by

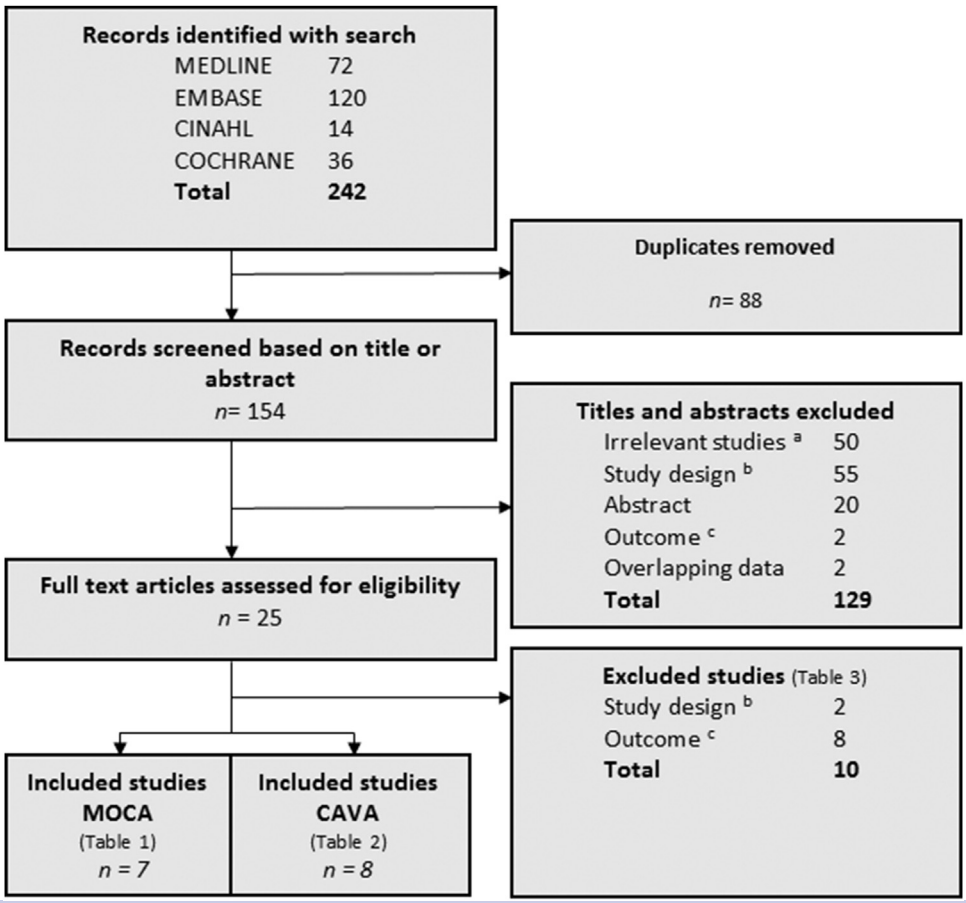

Fig 1. Flow chart of study selection. *CAVA,* Cyanoacrylate vein ablation; *CINAHL,* Cumulative Index to Nursing and Allied Health Literature; *MOCA,* mechanochemical ablation. [a]Studies describing irrelevant topics other than great saphenous vein (GSV) insufficiency. [b]Study designs such as reviews, case reports, and retrospective, ex vivo, and animal studies were excluded. [c]Studies not reporting the primary outcome (anatomic success at a minimum follow-up of 6 months) were excluded.

Almeida et al[22,23] overlap, but the studies describe different durations of follow-up and present unique data for at least one time interval. However, each cohort was included only once in all pooled analyses, and overlapping data were excluded from these analyses. Two included studies were randomized controlled trials (RCTs).[18,27] One RCT compared MOCA with radiofrequency ablation (RFA) in 170 patients,[18] and the other compared CAVA with RFA in 222 patients.[27] The remaining 13 included studies were prospective observational cohorts.[15-17,19-26,28,29] The included studies are summarized in Table I (MOCA) and Table II (CAVA). Studies that were excluded are listed in Table III.

According to the MINORS scoring scale, 14 studies[15-17,19-29] were of moderate methodologic quality (Fig 2). The RCT by Lane et al[18] had good methodologic quality. Blinding and prospective calculation of study size were infrequently reported. In 5 of 15 studies, whether all consecutive patients were included was not clear.[15-17,19,29] Loss to follow-up was not reported in one study[19] and was too high in five studies.[17,18,21,23,24] There was complete agreement between authors regarding the inclusion and exclusion of studies and the assessment of methodologic quality.

Technical details. The key technical aspects of the procedure were comparable between all studies, including local anesthesia, ultrasound-guided puncture, and positioning of the catheter relative to the saphenofemoral junction (SFJ). The minor technical differences were the duration of rotation at the start of the procedure and the starting distance to the SFJ. Two types of sclerosant were used in the MOCA studies. Polidocanol was used in three studies,[19-21] and sodium tetradecyl sulfate (STS) was used in two studies.[16,18] Two multicenter studies used STS in 84% of patients, but polidocanol was used in some of the participating centers for the remaining patients.[15,17] The reported concentration of polidocanol was 1.5% in two studies[15,17] and 2% in one study.[19] Two studies used 2% polidocanol for the most proximal 10 cm, followed by 1.5% for the remaining segment.[20,21] The applied concentration of STS was 1.5%[15-17] or 2%.[18]

Table I. Included studies of mechanochemical ablation (*MOCA*)

First author	Sample size, patients (limbs)	Study design	Inclusion criteria	Patients			
				Age, years, mean (range)	Sex, female, No. (%)	CEAP	GSV, mm
Bishawi,[15] 2014	126 (NR)	Prospective cohort	Symptomatic CEAP C2-C6 Reflux at SFJ >500 ms GSV diameter 5-12 mm (measured 2 cm below SFJ) Exclusion criteria Non-GSV reflux Deep or superficial vein hrombosis Previous venous intervention Significant peripheral arterial disease Limb infection	65	102 (81)	C1, 4% C2-3, 48% C4-6, 48%	7.3 (SD, 2.6)
Elias,[16] 2012	29 (30)	Prospective cohort	CEAP C2-C6 Reflux at SFJ >500 ms GSV ≤12 mm Exclusion criteria DVT Immobility Anticoagulation	54 (31-90)	17 (59)	C2, 77% C3, 7% C4, 16%	8.1 (range, 5.5-13)
Kim,[17] 2017	126	Prospective cohort	Symptomatic CEAP C2-C6 Reflux at SFJ >500 ms GSV diameter 5-12 mm (measured 2 cm below SFJ) Exclusion criteria Non-GSV reflux Deep or superficial vein thrombosis Previous venous intervention Significant peripheral arterial disease Limb infection	70 (SD, 14)	102 (81) 46 (70)	C1, 4% C2-3, 48% C4-6, 48%	7.6
Lane,[18] 2017	170	RCT	Symptomatic varicose veins Reflux ≥500 ms GSV ≥3 mm Exclusion criteria Recurrent varicose veins DVT Arterial disease Hypercoagulability	50	100 (59)	Median, 4	7

AVVQ, Aberdeen Varicose Vein Questionnaire; *CEAP,* Clinical, Etiology, Anatomy, and Pathophysiology classification; *DUS,* duplex ultrasound; *DVT,* deep venous thrombosis; *GSV,* great saphenous vein; *IQR,* interquartile range; *max,* maximum possible score; *MINORS,* Methodological Index for Non-Randomized Studies; *NR,* not reported; *RCT,* randomized controlled trial; *RFA,* radiofrequency ablation; *SD,* standard deviation; *SFJ,* saphenofemoral junction; *SSV,* small saphenous vein; *VCSS,* Venous Clinical Severity Score.
[a]Clinical success was defined as improved VCSS or AVVQ score.

Table I. Continued.

Intervention	Outcome	Follow-up	MINORS score (max)
MOCA Technical details 2 cm from SFJ Volume, pullback speed, and sclerosant: determined by each center (6 centers) Sclerosant used 16% polidocanol 84% STS (dosages NR) Postprocedural compression 98% postprocedural compression stockings (duration NR)	Anatomic success 3 months: 98% 6 months: 94% **Definition:** *complete GSV occlusion on DUS without any recanalization* Technical success 100% VCSS Baseline: 9 1 week: 6 3 months: 4 6 months: 3 Complications 10% thrombophlebitis 9% ecchymosis 1% hematoma	1 week (n = 125) 3 months (n = 100) 6 months (n = 89)	10 (16)
MOCA Technical details 2 cm from SFJ 2-3 seconds of rotation to cause a spasm Pullback speed, 0.1-0.2 mm/s Sclerosant used 1.5% STS Postprocedural compression 24 hours compression bandage 48 hours compression stocking (15-20 mm Hg) 10 days compression stocking (15-20 mm Hg) during day	Anatomic success 1 month: 96.7% 6 months: 96.7% **Definition:** *complete GSV occlusion on DUS without any recanalization* Technical success 100% Complications 10% ecchymosis 0% DVT 0% nerve injury 0% skin injury	8 (5-17) months	10 (16)
MOCA Technical details 2 cm from SFJ Pullback speed, 0.1-0.2 mm/s Sclerosant used 1.5% polidocanol (16%) 1.5% STS (84%) Postprocedural compression 98% postprocedural compression stockings (duration NR)	Anatomic success 1 week: 100% 3 months: 98% 1 year: 95% 2 years: 92% **Definition:** *complete GSV occlusion on DUS without any recanalization* Technical success 100% VCSS Baseline: 9 1 week: 6 3 months: 4 2 years: 3 Complications 10% thrombophlebitis 9% ecchymosis 1% hematoma	1 week (n = 126) 6 months (n = 89) 1 year (n = 79) 2 years (n = 65)	9 (16)
MOCA vs RFA Technical details 2 cm from SFJ 1-2 seconds of rotation to cause a spasm Pullback speed, 7 s/cm Sclerosant used 2% STS Postprocedural compression 2 weeks	Anatomic success 1 month: 93% vs 92% 6 months: 87% vs 93% No significant difference between MOCA and RFA **Definition:** *Complete GSV occlusion or occlusion of at least the proximal 5 cm on DUS* VCSS Baseline: 5 (4-7) 1 month: 2 (1-5) 6 months: 2 (1-5) No difference between MOCA and RFA AVVQ Baseline: 19.3 (13.2-28.7) 1 month: 12.8 (7.3-20.7; $P < .001$) 6 months: 10.8 (4.3-20.5; $P < .001$) No difference between MOCA and RFA Complications 3% thrombophlebitis 1% DVT 0% nerve injuries No difference between MOCA and RFA	1 month (n = 129) 6 months (n = 121)	23 (24)

Table I. Included studies of mechanochemical ablation (*MOCA*)

First author	Sample size, patients (limbs)	Study design	Inclusion criteria	Patients			
				Age, years, mean (range)	Sex, female, No. (%)	CEAP	GSV, mm
Özen,[19] 2014	63 (73)	Prospective cohort	CEAP C2-C6 Reflux at SFJ >500 ms GSV > 4.5 mm Exclusion criteria DVT Deep venous insufficiency Peripheral artery disease Allergy	45 (26-72)	43 (68)	C2, 63% C3, 20% C4, 6% C5, 8% C6, 3%	6 (range, 4.7-7.8)
van Eekeren,[20] 2014	92 (106)	Prospective cohort	Symptomatic CEAP C2-C6 Reflux at SFJ >500 ms GSV diameter 3-12 mm (measured 2 cm below SFJ) Exclusion criteria Pregnancy and lactation Anticoagulants Previous treatment of target vein DVT Coagulation disorders Severe renal or liver insufficiency Polidocanol allergy	52 (SD, 15)	62 (67)	C1, 1% C2, 36% C3, 33% C4, 30% C5, 2%	5.5 (IQR, 5-7)
Witte,[21] 2017	85 (104)	Prospective cohort	Symptomatic CEAP C2-C5 Reflux ≥500 ms GSV diameter 3-12 mm Exclusion criteria CEAP C6 Previous treatment of target vein Comorbid SSV or accessory saphenous vein incompetence Pregnancy and lactation DVT Coagulation disorders Severe renal or liver insufficiency Polidocanol allergy Anticoagulants use	51 (20-83)	70 (69)	C1, 1% C2, 34% C3, 30% C4, 30% C5, 2%	5.2 (range, 3.5-12.8)

Postprocedural compression therapy was applied in all studies, but the type and duration varied. The duration of compression was not reported in two studies,[15,17] was 48 hours in one study,[19] and was 2 weeks in another study.[18] The type of compression applied in these four studies was not specified. Elias and Raines[16] reported compression bandage for the first 24 hours, followed by compression stockings (15-20 mm Hg) for 48 hours, and thereafter followed by compression stockings (15-20 mm Hg) for 10 days only during the day.[16] van Eekeren et al[20] and Witte et al[21] used a schedule of 24 hours of compression stockings (30-40 mm Hg), followed by 2 weeks of compression stockings (30-40 mm Hg) only during the day.

Table I. Continued.

Intervention	Outcome	Follow-up	MINORS score (max)
MOCA Technical details No details Sclerosant used 2% polidocanol Postprocedural compression 48 hours compression bandage	Anatomic success 6 months: 94% 1 year: 95% 2 years: 95% **Definition:** *Complete GSV occlusion on DUS* Technical success 98% VCSS reduction 6 months: 3.2 (2-6) 1 year: 1.2 (1-3) 2 years: 1.1 (1-2; $P < .001$) Complications 13% thrombophlebitis 8% ecchymosis 18% induration 0% DVT 0% nerve injury 0% infection	6 months (n = 72) 1 year (n = 64) 2 years (n = 42)	6 (16)
MOCA Technical details 1.5 cm from SFJ Multiple seconds of rotation to cause a spasm Pullback speed, 7 s/cm Sclerosant used 2% polidocanol proximal 10 cm 1.5% polidocanol remaining segment Postprocedural compression 24 hours compression stocking (30-40 mm Hg) 2 weeks compression stocking (30-40 mm Hg) during day	Anatomic success 6 months: 93% 1 year: 88% **Definition:** *complete GSV occlusion on DUS without any recanalization* Technical success 99% Clinical success[a] 93% VCSS Baseline: 4 (3-5) 6 months: 1 (0-2) 1 year: 1 (0-1) AVVQ Baseline: 11.1 (8-19.2) 6 months: 6.6 (4-11) 1 year: 2.4 (0.5-6.2) Complications 3% thrombophlebitis 12% induration 9% hematoma 5% hyperpigmentation 0% DVT 0% nerve injury 0% skin injury	12 months	12 (16)
MOCA Technical details 2 cm from SFJ 2-3 seconds of rotation to cause a spasm Pullback speed 7 s/cm Sclerosant used 2% polidocanol proximal 10 cm 1.5% polidocanol remaining segment Postprocedural compression 24 hours compression stocking (30-40 mm Hg) 2 weeks compression stocking (30-40 mm Hg) during day	Anatomic success 6 months: 98% 1 year: 91.8% 2 years: 89.5% 3 years: 86.5% **Definition:** *complete GSV occlusion on DUS without any recanalization of a segment ≥10 cm* Technical success 99% Clinical success[a] 83% at 3 years VCSS Baseline: 4 (1-13) 6 months: 1 (0-6) 1 year: 1 (0-7) 3 years: 1 (0-7) AVVQ Baseline: 8.8 (2.5-29.4) 6 months: 4.1 (0-176.2) 1 year: 2.3 (0-22.4) 3 years: 5.6 (0-35.4) Complications 2% thrombophlebitis 14% induration 11% hematoma 5% hyperpigmentation	6 months (n = 98) 1 year (n = 87) 2 years (n = 71) 3 years (n = 48)	11 (16)

All of the studies on CAVA applied a similar procedural technique that involved local anesthesia, ultrasound-guided puncture of the GSV, and positioning of the catheter tip 3 to 5 cm proximal to the SFJ. Then, the SFJ was compressed by the probe, and the first 10 cm were treated, followed by compression of 5 seconds[24,25,29] or 3 minutes.[22,23,26-28] The latter five studies[22,23,26-28] injected two boluses of 0.08 to 0.09 mL of cyanoacrylate adhesive in the first segment, 1 cm apart, and the other studies used the standard dose of 0.03 mL/cm.[24,25,29] The remaining segment was treated with a dose of 0.03 mL/cm at a pull-back rate of 2 cm/s and was continuously compressed, or segments of 10 cm were compressed for 30 seconds each. In the study by Tekin et al,[29] a slightly higher dose of

Table II. Included studies of cyanoacrylate vein ablation (*CAVA*)

First author	Sample size, patients (limbs)	Study design	Inclusion criteria	Patients			
				Age, years, mean (range)	Sex, female, No. (%)	CEAP	GSV, mm
Almeida,[22] 2013	38 (38)	Prospective cohort	CEAP C2-C6 GSV 3-12 mm Exclusion criteria Previous venous intervention Allergy to cyanoacrylate Hypercoagulability Infection Insulin-dependent diabetes Right ventricular failure Deep vein insufficiency Arterial disease	51 (26-77)	29 (76)	C2, 37% C3, 18% C4, 42% C5, 0% C6, 3%	8 (4.1-12)
Almeida,[23] 2015	38 (38)	Prospective cohort	CEAP C2-C4 GSV 3-12 mm GSV reflux >500 ms Exclusion criteria Previous venous intervention Allergy to cyanoacrylate Hypercoagulability Infection Insulin-dependent diabetes Right ventricular failure Deep vein insufficiency Arterial disease	51 (26-77)	29 (76)	C2, 37% C3, 18% C4, 16% C6, 3%[a]	8.0 (4.1-12.0)
Bozkurt,[24] 2016	314 (314)	Prospective cohort	CEAP C2-C4 SFJ incompetence GSV reflux >500 ms GSV ≤15 mm Exclusion criteria DVT Infragenual deep vein incompetence SSV or accessory vein incompetence Pregnancy and lactation Coagulation disorders	41 (19-76)	158 (51)	C2, 72% C3, 23% C4, 5%	7.1 (SD, 1.7)
Çalik,[25] 2016	181 (215)	Prospective cohort	Symptomatic GSV or SSV incompetence CEAP C2-C5 GSV reflux >500 ms GSV 3-15 mm Exclusion criteria DVT Accessory saphenous vein insufficiency Active thrombophlebitis Deep vein incompetence Previous venous intervention Cancer Allergy to cyanoacrylate glue	38 (18-72)	110 (61)	NR	6.5 (4.3-14)

AVVQ, Aberdeen Varicose Vein Questionnaire; *CEAP,* Clinical, Etiology, Anatomy, and Pathophysiology classification; *DUS,* duplex ultrasound; *DVT,* deep venous thrombosis; *EVLA,* endovenous laser ablation; *GSV,* great saphenous vein; *max,* maximum possible score; *MINORS,* Methodological Index for Non-Randomized Studies; *NR,* not reported; *RCT,* randomized controlled trial; *RFA,* radiofrequency ablation; *SD,* standard deviation; *SFJ,* saphenofemoral junction; *SSV,* small saphenous vein; *VCSS,* Venous Clinical Severity Score.
Values are in mean (SD) or median (interquartile range [IQR]).
[a]Indicated as a protocol violation (C6 was one of the exclusion criteria).

0.05 mL/cm was used. The type of adhesive used was Sapheon VenaSeal[22,23,26-28] or Biolas VariClose.[24,25,29]

Most studies of CAVA did explicitly not apply postprocedural compression therapy[22,23,26,28] or only for the first 24 hours.[25,29] The remaining two studies did not report the use of compression therapy.[24,27]

Adjunctive treatment (ie, concomitant phlebectomy or sclerotherapy) in addition to GSV ablation was reported

Table II. Continued.

Intervention	Outcome	Follow-up	MINORS score (max)
CAVA with cyanoacrylate adhesive Technical details 4.0 cm from SFJ 30 seconds of compression Postprocedural compression No compression	Anatomic success 3 months: 98% 6 months: 95% 1 year: 92% **Definition:** *complete GSV occlusion on DUS without any recanalization of a segment ≥5 cm* VCSS Baseline: 6.1 (2.7) 1 year: 1.5 (1.4) Complications 18% thrombophlebitis 3% hyperpigmentation 3% cellulitis	6 months (n = 38) 1 year (n = 36)	12 (16)
CAVA with cyanoacrylate adhesive Technical details 4.0 cm from SFJ 30 seconds of compression Postprocedural compression No compression	Anatomic success 3 months: 98% 6 months: 95% 1 year: 92% 2 years: 92% **Definition:** *complete GSV occlusion on DUS without any recanalization of a segment ≥5 cm* VCSS Baseline: 6.1 (2.7) 6 months: 1.3 (1.2) 1 year: 1.3 (1.3) 2 years: 2.5 (NR) Complications 16% thrombophlebitis 3% hyperpigmentation 0% DVT	6 months (n = 38) 1 year (n = 36) 2 years (n = 24)	11 (16)
CAVA with cyanoacrylate adhesive vs EVLA Technical details 3.0 cm from SFJ 5 seconds of compression Postprocedural compression No compression	Anatomic success 1 month: 96.7% vs 87.1% 6 months: 96.7% vs 91.7% 12 months: 95.8 vs 92.2% **Definition:** *complete GSV occlusion and no flow on DUS without any recanalization of a segment ≥5 cm* Technical success 100% Complications 6% thrombophlebitis 1.6% hyperpigmentation 4.5% paresthesia only in EVLA group Ecchymosis more frequent in EVLA group	1 month (n = 283) 6 months (n = 274) 1 year (n = 266)	11 (16)
CAVA with *n*-butyl cyanoacrylate adhesive Technical details 3.0 cm from SFJ 5 seconds of compression Postprocedural compression Elastic compression (20-30 mm Hg) for 24 hours	Anatomic success 1 month: 100% 6 months: 97.6% **Definition:** *complete GSV occlusion (not compressible, no flow) on DUS without any patent segments ≥5 cm* Technical success 100% VCSS Baseline: 4.9 (1.2) 6 months: 1.4 (0.8) Complications 0.5% thrombophlebitis 0% DVT 0% nerve injury	7.5 (6-11) months	12 (16)

in seven studies (MOCA, four; CAVA, three)[15,17-19,24-26]; in seven studies, no adjunctive treatment was performed (MOCA, three; CAVA, four).[16,20-23,28,29] The proportion of patients that received any adjunctive treatment within the included studies ranged from 4.4% to 74%.[15,17-19,24-26] In one study in the CAVA group, performance of adjunctive treatment was not reported.[27]

Table II. Included studies of cyanoacrylate vein ablation (*CAVA*)

First author	Sample size, patients (limbs)	Study design	Inclusion criteria	Patients			
				Age, years, mean (range)	Sex, female, No. (%)	CEAP	GSV, mm
Chan,[26] 2017	29 (57)	Prospective cohort	GSV reflux Exclusion criterion Age <18 years	63 (39-80)	20 (69)	C3, 58% C4, 39% C5, 2% C6, 2%	7.1 (3.9-11.4)
Kolluri,[27] 2016	222	RCT	Symptomatic GSV Reflux >500 ms Exclusion criteria GSV >12 mm Previous venous intervention Non-GSV reflux Arterial disease DVT or pulmonary embolism	50 (26-71)	176 (79)	C2, 56% C3, 31% C4, 13%	6.5 (2.8-12)
Proebstle,[28] 2015	70	Prospective cohort	Symptomatic GSV reflux CEAP C2-4 GSV 3-10 mm Exclusion criteria Previous venous intervention DVT Thrombophlebitis GSV Hypercoagulability Allergy to cyanoacrylate	48 (22-72)	55 (79)	NR	7.8 (6.6-14)
Tekin,[29] 2016	62	Prospective cohort	Symptomatic GSV reflux CEAP C2-C6 GSV >5.5 mm Exclusion criteria GSV <5.5 or >13 mm Pregnancy DVT Thrombophlebitis	45 (29-72)	24 (38)	C2, 80% C3, 13% C4, 7%	7.5 (5.5-13)

Anatomic success. Initial technical success was described in six of seven of the MOCA studies and was 100% in three studies,[15-17] 99% in two,[20,21] and 98% in one.[19] The RCT by Lane et al[18] did not report technical success.[18] The closure rate at 6 months ranged from 87.1% to 98.1%.[15-21] After data of five included studies were pooled, the overall anatomic success at 6 months was 94.7% (95% confidence interval [CI],

Table II. Continued.

Intervention	Outcome	Follow-up	MINORS score (max)
CAVA with cyanoacrylate adhesive Technical details 4.0 cm from SFJ 30 seconds of compression Postprocedural compression Compression only when avulsion was performed	Anatomic success 1 week: 100% 1 month: 95.3% 6 months: 90.3% 1 year: 78.5% **Definition:** *complete GSV occlusion (not compressible, no flow) on DUS without any patent segments ≥5 cm* VCSS Baseline: 6.9 (3.5) 3 months: 2.4 (1.5) 6 months: 1.8 (1.7) 1 year: 1.7 (1.0) AVVQ Baseline: 23.7 (11.1) 3 months: 5.8 (5.6) 6 months: 4.7 (5.4) 1 year: 4.1 (2.8) Complications 3.5% DVT 2% access site infection 2% paresthesia	9 (1-13) months	12 (16)
CAVA with cyanoacrylate adhesive vs RFA Technical details No details Postprocedural compression NR	Anatomic success 3 months: 99% vs 95.4% 6 months: 99% vs 96.2% No significant difference between CAVA and RFA **Definition:** *complete GSV occlusion on DUS without patent segments >5 cm* VCSS Baseline: 5.5 vs 5.6 1 month: 2.3 vs 2.6 3 months: 1.9 vs 2.0 6 months: 1.5 vs 1.6 No significant difference between CAVA and RFA AVVQ Baseline: 18.9 (9.0) vs 19.4 (9.9) 1 month: 12.0 (7.1) vs 12.6 (8.3) 3 months: 11.6 (7.5) vs 10.7 (8.6) 6 months: 10.2 (7.2) vs 9.1 (6.9) Complications No difference in number and severity of events	1 month (n = 215) 3 months (n = 211) 6 months (n = 205)	22 (24)
CAVA with cyanoacrylate adhesive Technical details 5.0 cm from SFJ 30 seconds of compression Postprocedural compression No compression	Anatomic success 3 months: 94.3% 6 months: 92.9% 1 year: 92.9% (87%-99.1%) **Definition:** *complete GSV occlusion on DUS without patent segments >10 cm* Technical success 100% VCSS Baseline: 4.3 1 year: 1.1 ($P < .0001$) AVVQ Baseline: 16.3 (8.0) 1 month: 9.8 (7.6) 3 months: 7.6 (6.3) 6 months: 6.3 (5.8) 1 year: 6.7 (6.4; $P < .0001$) Complications 11% thrombophlebitis 1.4% ecchymosis 1.4% access site infection	6 months 3 months (n = 69) 1 year (n = 68)	13 (16)
CAVA with *n*-butyl cyanoacrylate adhesive Technical details 5.0 cm from SFJ Postprocedural compression No compression, elastic bandages on day 1	Anatomic success 1 month: 100% 3 months: 93.5% 6 months: 90.3%. **Definition:** *complete GSV occlusion on DUS* Complications 3.2% thrombophlebitis 1.6% hematoma 0% DVT	8 (0-13) months	10 (16)

91.3%-98.0%).[15,16,18,19,21] The closure rate at 12 months ranged from 87.7% to 95.2%.[17,19-21] After pooling of the data for three of the included studies, the overall anatomic success at 1 year was 94.1% (95% CI, 91.5-96.8%).[17,19,21] Fig 3 shows the pooled analysis of anatomic success at 6 months and 1 year. Anatomic success after a follow-up of 2 years was available in three studies and ranged from 89.5% to 95.0%.[17,19,21] The study

Table III. Excluded studies

First author	Sample size, patients (limbs)	Study design	Reason for exclusion
Mechanochemical ablation (MOCA) studies			
Bootun,[30] 2016	119 (119)	RCT	Total follow-up of 1 month
Deijen,[31] 2016	449 (570)	Prospective cohort	Total follow-up of 3 months
Lam,[32] 2016	87 (87)	RCT	Total follow-up of 6 weeks
Tang,[33] 2017	N/A	Review	Study design: review, no new data
Tang,[34] 2017	300 (345)	Prospective cohort	Total follow-up of 2 months
van Eekeren,[35] 2011	25 (30)	Prospective cohort	Total follow-up of 6 weeks
van Eekeren,[36] 2013	68 (68)	Prospective cohort	Total follow-up of 6 weeks, anatomic success not reported
Vun,[37] 2015	55 (57)	Retrospective cohort	Total follow-up of 6 weeks, retrospective study design
Cyanoacrylate vein ablation (CAVA) studies			
Alm,[38] 2014	193 (245)	Review	Review paper, author reports own nonprospective data
Gibson,[39] 2017	50 (50)	Prospective cohort	Total follow-up of 1 month

N/A, Not applicable; *RCT*, randomized controlled trial.

by Witte et al[21] had the longest follow-up and reported anatomic success of 86.5% at 3 years.[21]

Initial technical success was reported in three of eight CAVA studies and was 100%.[24,25,28] The remaining included studies did not report this outcome measure.[22,23,26,27,29] Complete closure rate at 6 months ranged from 89.5% to 99.1%.[22-29] Pooled analysis of seven included studies showed an overall anatomic success rate at 6 months of 94.8% (95% CI, 92.0%-97.6%).[23-29] Complete closure rates at 12 months ranged from 78.9% to 95.5% in five studies. The pooled anatomic success at 12 months of four studies was 89.0% (95% CI, 84.2-93.9%).[23,24,26,28] The pooled analysis of anatomic success at 6 months and 1 year is illustrated in Fig 4. The study by Almeida et al[23] reported a follow-up of 2 years and anatomic success in 92.0% of patients.

VCSS. The VCSS was reported in six of the seven MOCA studies.[15,17-21] Bishawi et al[15] reported that the mean VCSS decreased from 9 at baseline to 3 at 6 months. Kim et al[17] described a reduction in the mean VCSS from 9 at baseline to 3 at 2 years in the same cohort of patients. A significant reduction in median VCSSs from 5 (IQR, 4-7) to 2 (IQR, 1-5; $P < .0001$) at 6 months was reported by Lane et al[18] in an RCT comparing MOCA with RFA. The difference in VCSS results between the MOCA and RFA

	Bishawi 2014	Elias 2012	Kim 2017	Lane 2017	Ozen 2014	Van Eekeren 2014	Witte 2017	Almeida 2013	Almeida 2015	Bozkurt 2016	Calik 2016	Chan 2017	Kolluri 2016	Proebstle 2015	Tekin 2016
	Mechanochemical ablation														
1. A clearly stated aim	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	0	0	0	2	0	2	2	2	2	2	2	2	2	2	0
3. Prospective collection of data	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	2	0	0	0	0	0	0	0	0	2	1	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
7. Loss to follow-up less than 5%	2	2	1	1	0	2	1	2	1	1	2	2	2	2	2
8. Prospective calculation of the study size	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
Item 9-12 only for comparative studies															
9. An adequate control group				2								2			
10. Contemporary groups				2								2			
11. Baseline equivalence of groups				2								2			
12. Adequate statistical analyses				2								2			
TOTAL MINORS score	**10**	**10**	**9**	**23**	**10**	**12**	**11**	**12**	**11**	**11**	**12**	**12**	**22**	**13**	**10**
Maximum possible score	16	16	16	24	16	16	16	16	16	16	16	16	24	16	16
		good quality				moderate quality					poor quality				

Fig 2. Methodological Index for Non-Randomized Studies (*MINORS*) total score.

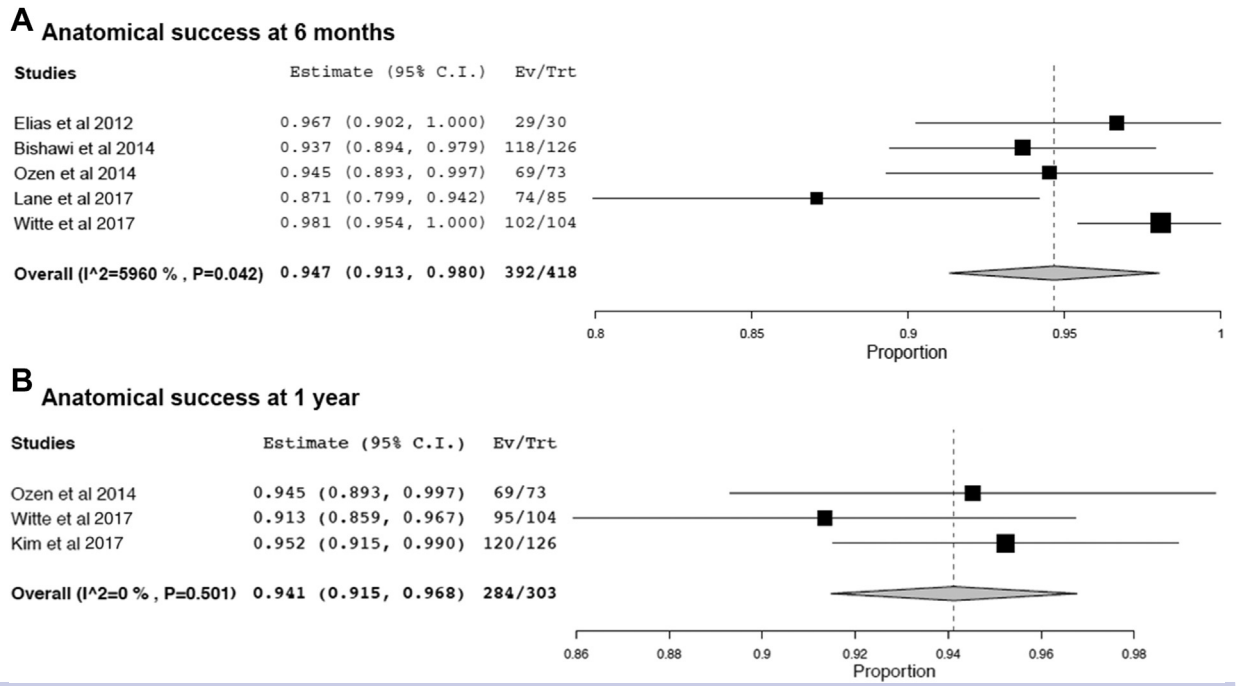

Fig 3. Pooled analysis of anatomic success at 6 months and 1 year for mechanochemical ablation (MOCA). *CI,* Confidence interval; *Ev/Trt,* observed number of events in the treatment group.

groups was not statistically significant. Özen et al[19] reported a significant ($P < .001$) reduction in the median (IQR) VCSSs of 3 (2-6), 1 (1-3), and 1 (1-2) at 6 months, 12 months, and 24 months, respectively, compared with preoperative values. van Eekeren et al[20] reported a median (IQR) baseline VCSS score of 4 (3-5) that reduced to 1 (0-2) at 6 months and remained at 1 (0-1) at 1 year after the intervention. Similar findings were reported by Witte et al,[21] with a baseline median (IQR) VCSS of 4 (1-13) that reduced to 1 (0-6) at 6 months, 1 (0-7) at 1 year, and 1 (0-7) after 3 years of follow-up.[21]

VCSS results were reported in six of eight of the included CAVA studies.[22,23,25-28] In the first report, by Almeida et al,[22] the mean (SD) VCSS reduced from 6.1

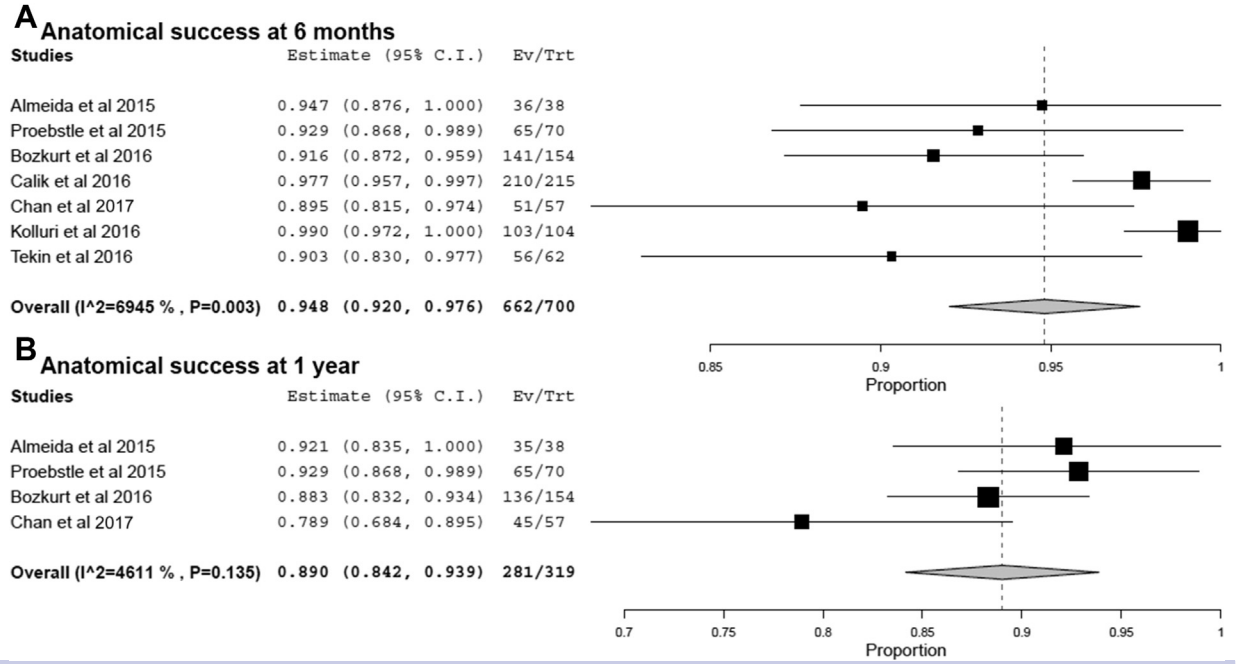

Fig 4. Pooled analysis of anatomic success at 6 months and 1 year for cyanoacrylate vein ablation (CAVA). *CI,* Confidence interval; *Ev/Trt,* observed number of events in the treatment group.

(2.7) at baseline to 1.5 (1.4) after 1 year of follow-up. In a second study with longer follow-up, the mean (SD) VCSSs were 6.1 (2.7), 1.3 (1.2), 1.3 (1.3), and 2.5 (SD not reported) at baseline, 6 months, 1 year, and 2 years, respectively.[23] Çalik et al[25] reported a reduction of the mean (SD) VCSS from 4.9 (1.2) at baseline to 1.4 (0.8) at 6 months. The mean (SD) VCSSs were 6.9 (3.5) at baseline, 2.4 (1.5) at 3 months, 1.8 (1.7) at 6 months, and 1.7 (1.0) at 1 year of follow-up in the study by Chan et al.[26] In an RCT of CAVA vs RFA, the mean (SD) VCSSs were 5.5 (2.6) vs 5.6 (2.6) at baseline, 2.3 (1.7) vs 2.6 (2.0) at 1 month, 1.9 (1.6) vs 2.0 (2.0) at 3 months, and 1.5 (1.8) vs 1.6 (1.9) at 6 months.[27] The difference between the CAVA and RFA groups was not statistically significant. Finally, a significant reduction in the mean VCSSs was found from 4.3 at baseline to 1.1 at 1 year ($P < .0001$) by Proebstle et al.[28]

In summary, all studies, both on MOCA and CAVA, reporting VCSSs found a significant or clinically relevant reduction in these scores after treatment compared with baseline values.

AVVQ. Three of seven MOCA studies reported the AVVQ score.[18,20,21] In the RCT by Lane et al,[18] AVVQ scores were significantly lower after 1 month (median, 12.8; range, 7.3-20.7) and 6 months (median, 10.8; range, 4.3-20.5) compared with baseline values (median, 19.3; range, 13.2-28.7). The difference in AVVQ scores between the MOCA and RFA groups was not statistically significant.[18] van Eekeren et al[20] also reported a significant reduction in AVVQ scores from 11.1 at baseline (IQR, 8-19.2) to 6.6 (IQR, 4-11) at 6 months and 2.4 (IQR 0.5-6.2) at 1 year. Finally, Witte et al[21] reported a significant reduction from 8.8 (IQR, 2.5-29.4) at baseline to 4.1 (IQR, 0-176.2) at 6 months, 2.3 (IQR, 0-22,4) at 1 year, and 5.6 (IQR, 0-35.4) at 3 years.

Of the studies on CAVA, three reported the AVVQ score.[26-28] Chan et al[26] reported a significant reduction in mean (SD) AVVQ score compared with baseline (23.7 [11.1]) to 5.8 (5.6), 1.8 (1.7), and 1.7 (1.0) at 3 months, 6 months, and 12 months, respectively. Kolluri et al[27] reported a reduction in mean (SD) AVVQ score from baseline (18.9 [9.0]) to 12.0 (7.1), 11.6 (7.5), and 10.2 (7.2) at 1 month, 3 months, and 6 months, respectively. AVVQ scores in the CAVA and RFA groups were comparable in this RCT. In the study by Proebstle et al,[28] a significant reduction from 16.3 (SD, 8.0) at baseline to 6.7 (SD, 6.4) at 1 year was reported. At 1 month, 3 months, and 6 months, the mean (SD) AVVQ score was also significantly reduced to 9.8 (7.6), 7.6 (6.3), and 6.3 (5.8), respectively.

Complications. Complications were reported in all studies of MOCA and CAVA, although the type and rate of complications described varied. The most frequently reported complications in the MOCA studies were induration (12%-18%),[19-21] thrombophlebitis (2%-13%),[15,17-21] and ecchymosis (8%-10%)[15-17,19] or hematoma (1%-11%).[15,17,20,21] Less frequently reported were deep venous thrombosis (0%-1%)[16,18-20] and hyperpigmentation (5%).[20,21] No nerve injuries, skin injuries, or infections were reported in the included MOCA studies.

In the CAVA studies, the most reported complications were thrombophlebitis (0.5%-18%)[22-25,28,29] and hyperpigmentation (1.6%-3%).[22-24] Other reported complications included deep venous thrombosis (0%-3.5%),[23,25,26,29] access site infection or cellulitis (1.4%-3%),[22,26,28] and ecchymosis or hematoma (1.4%-1.6%).[28,29] Nerve injury or paresthesia was rare (0%-2%).[24-26] Bozkurt and Yilmaz[24] reported that ecchymosis occurred more frequently in the endovenous laser ablation (EVLA) group, but no data were reported to support their statement. They also reported 4.5% paresthesia, 3.2% temporary and 1.3% permanent, which occurred only in the EVLA group. The RCT by Kolluri et al[27] reported no difference in the number and severity of complications between CAVA and RFA without further specification of the complications that occurred.

DISCUSSION

In this systematic review and meta-analysis of the available literature on two novel nonthermal venous ablation techniques, MOCA and CAVA, anatomic success was 94.7% and 94.9% at 6 months and 94.1% and 89.6% at 1 year, respectively. Although these data seem to suggest that MOCA has slightly better results in effectiveness and GSV closure rates, no direct comparison has been made between MOCA and CAVA so far, and further data, preferably from RCTs, are required before any conclusions can be made. One could argue that anatomic success is not the same as clinical success. However, the clinical success was also analyzed using the VCSS and AVVQ assessments, which both improved significantly and remained improved at all follow-up intervals in all studies reporting these patient-reported outcomes. Among the main advantages over established treatment modalities for GSV incompetence are that no tumescent anesthesia is needed, leading to reduced procedure time, and increased comfort of the patient. Furthermore, no thermal energy, with an associated risk of nerve injury, is applied.

A recent systematic review analyzed the literature and compared outcomes of UGFS with EVLA, RFA, and conventional surgery.[11] The main findings were as follows:

1. Anatomic success rates were consequently lower in the UGFS groups (<85% at 1 year) compared with EVLA or RFA (>90% at 1 year).
2. Despite the lower anatomic success rates, patient-reported outcomes and clinical symptoms improved in all treatment groups to a comparable extent.
3. All techniques are extremely safe, with a very low rate of (serious) complications.
4. Costs are lower in the USGF groups, although a formal cost-effectiveness analysis was not performed.

5. There was considerable heterogeneity in the technique of UGSF and EVLA applied between trials, and techniques currently considered standard practice were different in the included trials.

These findings are in accordance with an earlier published Cochrane systematic review from 2014 on the same topic.[5]

When these findings are compared with the anatomic success rates found in this paper for MOCA and CAVA, these novel techniques at least seem promising. CAVA demonstrated higher closure rates at 1 year (89.6%) than those found for UGFS in the systematic review mentioned before (<85%). However, although not directly compared, CAVA seems to perform slightly worse than MOCA, RFA, and EVLA. Nevertheless, further data from RCTs are needed before any conclusions can be drawn.

There are some limitations to the strength of the conclusions that can be drawn from this meta-analysis. Although all included studies were prospective studies, including two RCTs,[18,27] methodologic quality was not higher than moderate for most of the studies. Baseline VCSS and AVVQ scores varied between studies, which implies differences in severity of disease of included patients in the studied cohorts.

The definition of anatomic success varied between studies. For example, some studies considered a GSV without recanalization of ≥10 cm as anatomic success, another study considered an occluded proximal segment of at least 5 cm as anatomic success, whereas many others considered complete closure without any recanalization as anatomic success. The impact of these different definitions on long-term outcome is unclear.

The use of adjunctive treatment also deserves further discussion as it is another factor contributing to heterogeneity among the included studies. Although in approximately half of the studies no adjunctive treatment was applied, in the remaining studies, 4% to 74% of the patients received additional treatment of varicose veins. These adjunctive therapies can have a significant impact on patient-reported outcomes and quality of life, and future studies comparing techniques for GSV ablation should make sure that adjunctive treatments between study groups are comparable and well documented.

Furthermore, most of the studies for MOCA and CAVA had only a short follow-up of 6 months to 1 year. Many studies were industry driven or industry sponsored, and publication bias cannot be ruled out. High-quality studies with long-term follow-up are needed to provide a firm evidence base for these treatment modalities and to determine their position relative to the more established therapies, such as RFA and EVLA.

Another point of interest is the difference in type and dose of sclerosant used between studies on MOCA. Dose-finding studies for MOCA are currently being performed, and an interim analysis demonstrated that 1% polidocanol leads to inferior results compared with 2% or 3% polidocanol.[32] Final results of this dose-finding trial are expected shortly.

Since the introduction of MOCA, several procedural changes have been introduced. Although the technical procedure within the included studies did not differ, the latest recommendation from the manufacturer includes a minimum of 3 seconds of rotation time under the SFJ to create a vasospasm, and re-treatment is advised if the proximal 10 cm is not occluded after the first run. For CAVA, there are also minor differences in applied technique, especially concerning the first segment distal to the SFJ. Future studies are needed to further optimize the technique.

Complications were reported in all studies, but the definitions and reporting of these complications varied. However, none of the included studies reported serious complications. Deep venous thrombosis was rare and reported in only two studies, both involving one patient in each study.[18,26] However, the included studies were generally too small for any conclusions to be drawn about rare complications, such as deep venous thrombosis. More frequently reported were thrombophlebitis and ecchymosis or hematoma, which were generally self-limited.

One of the advantages of NTA methods could be the avoidance of heat production, thereby further decreasing the risk of nerve injury, making these techniques especially interesting for below-knee GSV treatment. Although high rates of nerve injury of up to 39% were reported after below-knee stripping,[40] such rates were not encountered after endovenous thermal ablation, for which rates similar to above-knee ablation of the GSV (3%-4%) were described.[41] None of the studies included in this paper reported whether below-knee GSVs were treated, and no subgroup analyses of these patients were performed. Theoretically, the risk of nerve injury could be further decreased using NTA techniques because no heat is produced and there is no risk of nerve injury due to areas were tumescent is administered inadequately. However, to the knowledge of the authors, this theoretical advantage is not yet confirmed in high-quality trials.

CONCLUSIONS

The currently available evidence demonstrated high anatomic success rates for MOCA and CAVA comparable to those previously reported for RFA and EVLA. These results are promising for these novel techniques that could serve as alternatives for thermal ablation techniques. However, to determine their exact role in clinical practice, high-quality RCTs comparing these novel modalities with well-established techniques are required.

AUTHOR CONTRIBUTIONS

Conception and design: CGV, CU, MS
Analysis and interpretation: CGV, CU, JB, CJV, AN, MS
Data collection: CGV, CU, MS
Writing the article: CGV, CU, MS
Critical revision of the article: CGV, CU, JB, CJV, AN, MS
Final approval of the article: CGV, CU, JB, CJV, AN, MS
Statistical analysis: CGV, CU
Obtained funding: Not applicable
Overall responsibility: MS

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