

Comparative analysis of the results of cyanoacrylate ablation and radiofrequency ablation in the treatment of venous insufficiency

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ABSTRACT

Background: Varicose vein treatment has shifted to less invasive techniques owing to the complications associated with traditional treatment. The present study was designed to compare the effectiveness of cyanoacrylate ablation (CAA) with radiofrequency ablation (RFA).

Methods: Patients who had undergone RFA vs CAA (634 vs 246 patients) to treat great saphenous vein (GSV) insufficiency during a 5-year period were included in the present study. The preoperative and postoperative CEAP (clinical, etiologic, anatomic, pathophysiologic) class, symptoms, recurrence, and Doppler ultrasound findings were compared.

Results: All the veins in both groups were occluded at day 5. The 1-month closure rates were 97.3% and 98.7% for RFA and CAA, respectively. The overall postoperative closure rates at 5 years were 93.1% and 91.1% for RFA and CAA, respectively. The postoperative symptoms, CEAP class, and Doppler ultrasound findings were similar in both groups. The 5-year symptom-free survival rates were 73.5% and 72.0% in the RFA and CAA groups, respectively. The venous clinical severity scores had decreased from 5.9 ± 1.2 to 0.9 ± 0.8 and 5.8 ± 0.9 to 0.8 ± 0.6 in the RFA and CAA groups, respectively. The Aberdeen varicose vein questionnaire scores had decreased from 19.7 ± 5.5 to 4.8 ± 1.5 in the RFA group and from 18.9 ± 5.8 to 4.9 ± 1.4 in the CAA group.

Conclusions: CAA seems to be the ideal treatment for GSV insufficiency because it is suitable for most patients and is nonthermal and nontumescent, with satisfactory results comparable to those with RFA. Long-term outcomes and cost analyses from larger series are required to confirm our findings. (J Vasc Surg Venous Lymphat Disord 2021;■:1-8.)

Keywords: Chronic venous insufficiency; Cyanoacrylate ablation; Radiofrequency ablation; Varicose veins

Chronic venous insufficiency (CVI) is a common disease associated with significant morbidity. The worldwide prevalence of CVI is >80%, and CVI causes a wide range of symptoms, from leg discomfort to ulcers.¹ The high prevalence of CVI and the wide range of symptoms also result in considerable economic burden.² The classic treatment, high ligation and stripping with the patient under general or spinal anesthesia, has decreased in popularity because of complications such as hematoma and paresthesia and endovenous ablation techniques have increased in popularity.³ Endovenous

ablation techniques have been associated with shorter recovery times and have been shown to result in greater long-term success rates.^{3,4} However, the disadvantages of thermal ablation techniques include postoperative pain and discomfort, skin bruises, paresthesia, burns caused by thermal damage, and the requirement for tumescent anesthesia. Therefore, an increasing need has emerged for the development of nonthermal, nontumescent (NTNT) options.

Cyanoacrylates were developed in the late 1940s and have been used for medical applications for ~40 years.⁵⁻⁷ N-butyl cyanoacrylate (NBCA), which now includes low viscosity variants, has been applied in the development of nontumescent techniques for endovenous ablation. The absence of reports of delayed type hypersensitivity reactions and the minimization of glue propagation to the deep venous system through instant polymerization of low viscosity NBCA are favoring use of low viscosity NBCA produced in Turkey.^{8,9} Thus, in the present study, we compared the effectiveness of low viscosity cyanoacrylate ablation (CAA) for endovenous ablation with the effectiveness of radiofrequency ablation (RFA).

METHODS

Study design. The local ethics committee approved the present retrospective review of patient records, and all included patients had provided written informed consent

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before undergoing either RFA or CAA. We reviewed the medical records of the patients who had undergone RFA (ClosureFast; Medtronic, San Jose, Calif) or CAA (Vena-Block Venous Closure System; Invamed, Ankara, Turkey) for great saphenous vein (GSV) insufficiency during a 5-year period. The patients were informed about both techniques and were allocated to either treatment in accordance with surgeon experience and patient preference. Mini-phlebectomy and sclerotherapy were simultaneously applied to varicose tributaries. Patients with bilateral disease received the same treatment simultaneously. The pre- and postoperative CEAP (clinical, etiologic, anatomic, pathophysiologic) class, symptoms, recurrence, and Doppler ultrasound findings for the two groups were compared. The predictive factors for postoperative symptom recurrence, CEAP class, deep venous insufficiency (DVI), perforator incompetence (PI), and early symptom recurrence were calculated. Symptomatic patients with a CEAP class of C2 to C6 and GSV diameter >5.5 mm with reflux exceeding 0.5 second who had undergone RFA or CAA were included in the present study. The exclusion criteria were reflux of any vein except for the GSV, GSV diameter >15 mm, pregnancy, acute thrombophlebitis, acute deep vein thrombosis (DVT), peripheral arterial disease, local infection at the puncture site, and immobility. Because hypersensitivity to cyanoacrylate seems to be the only absolute contraindication to CAA, patients with a known sensitivity were excluded.¹⁰ Also, the venous clinical severity score (VCSS) and Aberdeen varicose vein questionnaire (AVVQ) were assessed pre- and postoperatively. The CAA and RFA procedures were performed as described for all patients.

CAA procedure. The VenaBlock Venous Closure System (Invamed) includes 3 mL of low viscosity NBCA and a disposable delivery kit. GSV was accessed using a 6F introducer set with ultrasound guidance. A 0.035-in. × 150-cm guidewire was introduced through a 6F introducer sheath and positioned 6 cm below the saphenofemoral junction (SFJ). The delivery catheter was then placed 3 cm below the SFJ through the long introducer sheath, and the injection gun was connected to the delivery catheter. Pressure over the SFJ was applied, and NBCA was injected continuously. Each push of the trigger injects 0.3 mL of NBCA. The trigger was pushed for 5 seconds, and the delivery catheter was retracted at 2 cm/s. Pressure was applied over each 10-cm segment with the Doppler ultrasound probe, and the pressure over the SFJ was not relaxed until the end of the procedure.

RFA procedure. The ClosureFast system (Medtronic) was used in accordance with the instructions provided by the manufacturer.

Postprocedure management and follow-up. After completion of each procedure, compression bandages were applied to all patients, who were discharged the

ARTICLE HIGHLIGHTS

- **Type of Research:** A retrospective analysis of patient registry data
- **Key Findings:** During a 5-year period, 634 patients had undergone radiofrequency ablation (RFA) and 246 had undergone cyanoacrylate ablation (CAA) using a low viscosity n-butyl cyanoacrylate for great saphenous vein insufficiency. Postoperatively, the overall closure rates at 5 years were 93.1% and 91.1% for RFA and CAA, respectively, with no differences between the two groups regarding the postoperative symptoms, CEAP (clinical, etiologic, anatomic, pathophysiologic) class, or Doppler ultrasound findings.
- **Take Home Message:** RFA and CAA with a low viscosity n-butyl cyanoacrylate provided comparable results at 5 years.

same day. Although compression stockings are not routinely recommended after CAA, we recommended compression stockings for the patients in both groups. Also, venoactive medications, which could have included micronized purified flavonoid fraction, calcium dobesilate, or oxerutin, were prescribed for 6 months after treatment. The activity of the patients was not restricted after the procedure.

All the patients were scheduled follow-up at 5 days and 1, 6, 12, 24, 36, 48, and 60 months after treatment. Doppler ultrasound was performed to determine the success of ablation. The CEAP clinical class, symptoms, VCSS, and AVVQ score were recorded at all the follow-up visits. Treatment success was defined as closure of the GSV with no discrete patent segment of >5 cm in the treated portion of the GSV.

Statistical analysis. Statistical analyses were performed using SPSS, version 21 (IBM Corp, Armonk, NY). $P < .05$ was considered to indicate statistical significance. Categorical variables are reported as frequencies and proportions and continuous variables as the mean, average, and standard deviation. The patient characteristics and hospital outcomes were compared using the t test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Differences between pre- and postoperative symptom status were compared using linear trend analyses. Event-free survival and closure rates were evaluated using Kaplan-Meier analysis. The correlates of event-free survival and risk factors affecting postoperative symptom development were analyzed using a Cox proportional hazards model and multivariate stepwise logistic regression analyses.

RESULTS

During a 5-year period, 634 had undergone RFA and 246 patients had undergone CAA for GSV insufficiency

Table I. Preoperative demographic, operative, and postoperative variables

Variable	RFA group	CAA group	P value
Age, years	48.6 ± 10.12	49.8 ± 8.1	.753
Sex			.699
Male	277	108	
Female	357	138	
Extremity			.821
Unilateral	550	205	
Bilateral	84	41	
Occupation ^a			.405
No	133	81	
Yes	501	165	
Family history ^b			.827
No	340	138	
Yes	294	108	
DVT			.613
No	516	208	
Yes	118	38	
DM			.723
No	549	210	
Yes	85	36	
HTN			.878
No	449	183	
Yes	185	63	
Smoking			.602
No	402	129	
Yes	232	117	
Alcohol			.516
No	582	222	
Yes	52	24	
Preoperative DVI			.152
No	498	206	
Yes	136	40	
Preoperative CEAP class			.122
<3	114	66	
≥3	520	180	
Mini-phlebectomy/sclerotherapy			.556
No	536	204	
Yes	98	42	
Postoperative symptoms			.643
No	426	172	
Yes	208	74	
Postoperative SFI			.87
No	590	224	
Yes	44	22	
Postoperative PI			.104
No	613	242	
Yes	21	4	

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Table I. Continued.

Variable	RFA group	CAA group	P value
Postoperative CEAP class			.763
<3	484	183	
≥3	150	63	

CAA, Cyanoacrylate ablation; CEAP, clinical, etiologic, anatomic, pathophysiologic; DM, diabetes mellitus; DVI, deep venous insufficiency; DVT, deep vein thrombosis; HTN, hypertension; PI, perforator incompetence; RFA, radiofrequency ablation; SFI, saphenofemoral insufficiency.
Data presented as mean ± standard deviation or number.
^aRequiring prolonged standing and/or low physical activity.
^bA family history of venous insufficiency.

and were included in the present study. The mean age of the patients was 48.9 ± 11.7 years (range, 30-70 years), and the mean follow-up time was 26.1 ± 13.2 months. Of the 880 patients, 385 were men and 495 were women. All the patients had had signs or symptoms of venous insufficiency, most often varicose veins, in at least one extremity. Additional symptoms included leg restlessness, pain, night cramps, itching, skin changes, and bleeding. Most patients had had a CEAP class of ≥ 3 . Additional demographic and clinical details, including patients with an occupation requiring prolonged standing and low physical activity and a positive family history of venous insufficiency, are presented in Table I. No significant differences were found between the two groups in the baseline characteristics.

In the RFA and CAA groups, all the veins were occluded at 5 days after treatment. The 1-month closure rates were 97.3% and 98.7% for the RFA and CAA groups, respectively. No statistically significant difference was found between the overall postoperative closure rates at 5 years (93.1% vs 91.1% for the RFA and CAA groups, respectively; $P = .313$). The type of ablation technique had no significant effects on the occurrence of postoperative symptoms or CEAP class. The effectiveness of the two techniques in the treatment of saphenofemoral insufficiency was not significantly different (Table I).

Predictors of postoperative symptom recurrence. The univariate and multivariate significant predictors of postoperative symptom recurrence were bilateral limb disease ($P = .009$), preoperative CEAP class of ≥ 3 ($P = .018$), occupation requiring prolonged standing and low

physical activity ($P = .001$), and a positive family history ($P = .037$; Table II).

Predictors of postoperative CEAP class. The univariate predictors of the postoperative CEAP class were female sex, preoperative CEAP class of ≥ 3 , bilateral limb disease, prior DVT, and older age ($P < .05$). The multivariate predictors were bilateral limb disease ($P = .002$) and prior DVT ($P = .004$; Table III).

Predictors of postoperative DVI. The univariate predictors of postoperative DVI were female sex, preoperative DVI, and occupation requiring prolonged standing and low physical activity. The only significant multivariate predictor was preoperative DVI ($P < .001$; Supplementary Table I).

Predictors of postoperative perforator incompetence. The univariate predictors of postoperative perforator incompetence (PI) were older age, occupation requiring prolonged standing and low physical activity, preoperative CEAP class of ≥ 3 , preoperative PI, and a positive family history. The multivariate predictors of postoperative PI were age ≥ 60 years ($P < .001$), occupation requiring prolonged standing and low physical activity ($P < .001$), preoperative CEAP class of ≥ 3 ($P = .015$), and preoperative PI ($P < .001$; Supplementary Table II).

Predictors of early (<1 year) postoperative symptom recurrence. The univariate predictors of early (<1 year) symptom recurrence were smoking, hypertension, CCA, preoperative PI, and a positive family history. No multivariate predictors were identified (Table IV). The cumulative

Table II. Predictors of postoperative symptom recurrence from univariate and multivariate analyses

Predictive factor	Univariate P value	OR	95% CI	Multivariate P value
Bilateral disease	<.001	2.512	1.271-4.545	.009
Preoperative CEAP class ≥ 3	<.001	4.652	1.009-9.411	.018
Occupation ^a	<.001	5.650	3.542-9.025	.001
Family history ^b	.042	3.215	2.392-4.326	.037

CEAP, Clinical, etiologic, anatomic, pathophysiologic; CI, confidence interval; OR, odds ratio.
^aRequiring prolonged standing and/or low physical activity.
^bA family history of venous insufficiency.

Table III. Predictors of postoperative CEAP class on univariate and multivariate analyses

Predictive factor	Univariate <i>P</i> value	OR	95% CI	Multivariate <i>P</i> value
Preoperative CEAP ≥ 3	<.001	1.446	0.379-4.912	.886
Female sex	<.001	1.555	0.222-3.424	.966
Age ≥ 60 years	.031	1.314	0.284-3.878	.991
Bilateral disease	.029	5.113	3.111-9.004	.002
DVT	.027	8.112	2.421-17.003	.004

CEAP, Clinical, etiologic, anatomic, pathophysiologic; CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio.

5-year symptom-free survival rate was $72.6\% \pm 0.48\%$ (Supplementary Fig). The comparative 5-year symptom-free survival rates were $72.0\% \pm 0.1\%$ and $73.5\% \pm 0.6\%$ in the CAA and RFA groups, respectively, with no significant differences between the two groups ($P = .219$; Fig). In the RFA and CAA groups, the VCSS (RFA, $P = .017$; CCA, $P = .023$) and AVVQ scores (RFA, $P = .031$; CCA, $P = .038$) had improved postoperatively compared with baseline, with no statistically significant differences between the two techniques (VCSS, $P = .72$; AVVQ score, $P = .66$; Table V).

DISCUSSION

The side effects of thermal tumescent techniques have emerged and stimulated the need for NTNT techniques. Sclerosing agents such as tetradecyl sulfate and polidocanol have been used for ablation. However, the high treatment failure rate of liquid sclerosants led to the development of foam sclerotherapy and Tessari described an easy way to produce stable foam.¹¹⁻¹⁴ Tessari described an easy method for producing stable foam. A 90% approximate GSV occlusion rate was achieved with ultrasound guidance or catheter-directed application.^{15,16} Foam sclerotherapy is less effective than RFA or endovenous laser ablation but has been shown to improve patients' quality of life.^{3,17}

An alternative NTNT ablation technique with a quickly polymerizing adhesive liquid, NBCA, has been described. When NBCA encounters anions, it becomes solid.¹⁸ Kailasnath and Chaloupka¹⁹ described the three stages of cyanoacrylate polymerization in the common carotid artery of swine. In the first phase, tensile forces were increased within <10 seconds. In the second phase, the tensile forces were stabilized up to 1 minute. Finally, the

tensile forces increased exponentially in the polymerization phase.¹⁹ NBCA application causes endothelial inflammation and, eventually, fibrosis of the vein.

The first experiment on swine epigastric veins showed complete occlusion.²⁰ Subsequently, the first clinical trial was performed in which Almeida et al,²¹ reported an occlusion rate of 92% at 24 months in a group of 38 patients. The VCSS had also improved without any complications.²¹ Similarly, a prospective, multicenter European study in which 70 patients were enrolled showed an occlusion rate of 92.9% at 12 months.⁹

In the VeClose trial (VenaSeal Saphoon closure system pivotal study), a multicenter, randomized controlled trial in which 222 patients were enrolled, the occlusion rates for CAA and RFA were 94.4% and 91.9% at 36 months, respectively ($P = .75$).²² Recently, a 60-month follow-up extension study of the VeClose patients was reported.²³ In that study, 89 patients were observed. The primary outcome was no new GSV insufficiency between the 36- and 60-month follow-up visits. At 60 months, complete closure of the GSV was 94.6% for the CAA group and 100% for the RFA group ($P = .292$).²³

It has been reported that the occurrence of pain during venous access and periprocedural pain are similar between the CAA and RFA groups.^{24,25} Ecchymosis was not observed or was less after CAA than after RFA.^{24,25} Another study comparing CAA, RFA, and endovenous laser ablation reported that 61.3% of the patients who had undergone CAA had not experienced pain during the procedure.²⁶ In contrast, all the patients in the other two groups had reported pain.²⁶ Statistically significant differences were not reported for complications such as DVT, pulmonary embolism, and phlebitis.^{24,26} In the VeClose trial, phlebitis was more common in the CAA

Table IV. Predictors of early (<1 year) postoperative symptom recurrence on univariate and multivariate analyses

Predictive factor	Univariate <i>P</i> value	OR	95% CI	Multivariate <i>P</i> value
Cyanoacrylate	.047	0.724	0.312-0.966	.201
Smoking (yes vs no)	.049	1.104	0.311-2.917	.396
Hypertension (yes vs no)	.036	0.616	0.105-1.299	.314
Family history ^a (yes vs no)	.006	0.917	0.189-3.246	.161
Preoperative PI (yes vs no)	.028	0.419	0.183-0.916	.216

CI, confidence interval; OR, odds ratio; PI, perforator incompetence.

^aA family history of venous insufficiency.

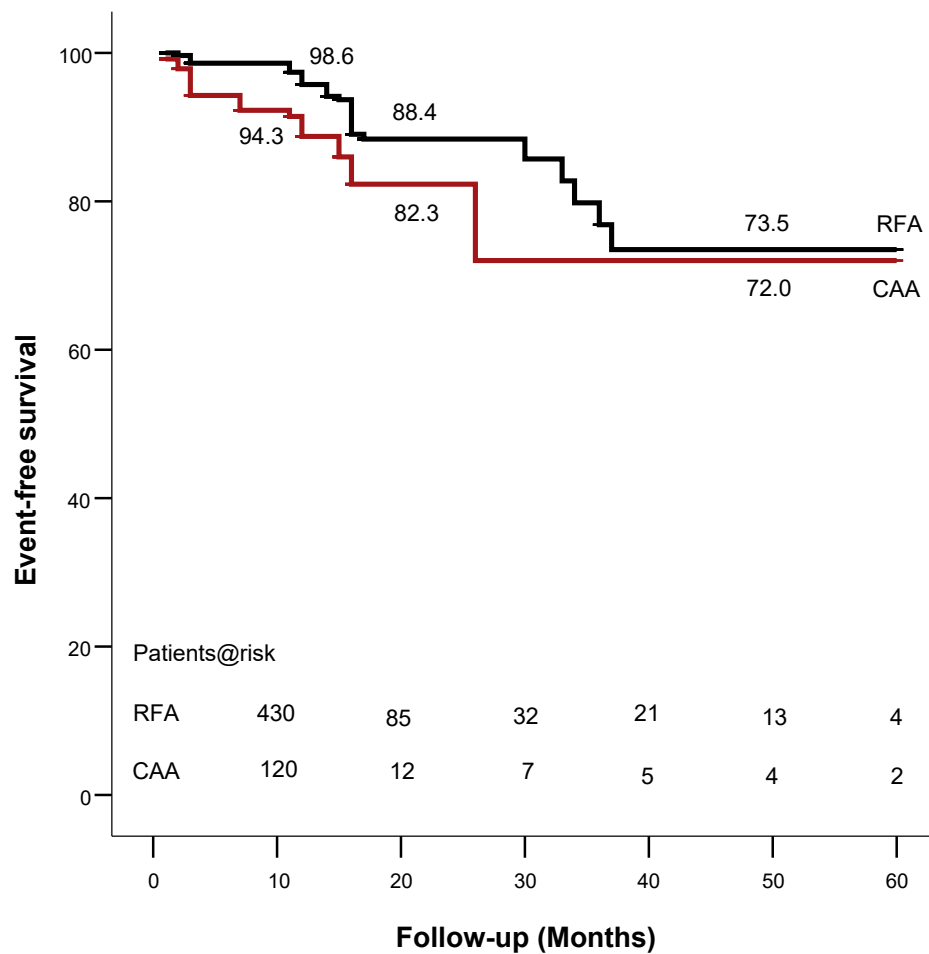


Fig. Comparative event-free survival rates for the radiofrequency ablation (RFA) and cyanoacrylate ablation (CAA) groups. The standard error was never >10%.

group at 3 months ($P = .36$). Phlebitis was treated successfully with ibuprofen in both the CAA and the RFA groups.²⁴

The main difference in the present study was the viscosity of the NBCA used. The polymerization time of cyanoacrylate is dependent on the viscosity. Because low viscosity NBCA polymerizes immediately, the delivery catheter was positioned 3 cm below the SFJ.²⁵⁻²⁷ The catheter was placed 5 cm below the SFJ to prevent postablation thrombus extension in the previously cited studies.⁹ In other studies, the distance was increased to provide safe glue propagation toward the SFJ because of the high viscosity of the NBCA.

Delayed type hypersensitivity is another complication encountered after CAA. Some studies have reported hypersensitivity reactions; however, the 60-month extension study of the VeClose trial reported none.^{23,28,29} In our study, we also observed no delayed type hypersensitivity reactions. Also, to the best of our knowledge, no delayed type hypersensitivity reactions have been reported with the low viscosity NBCA used in our study.⁸

Another critical point emphasized in the present study is the univariate and multivariate significant predictors of postoperative symptom recurrence. The use of CAA was a univariate predictor of early symptom recurrence,

Table V. Preoperative and postoperative disease severity and effects on quality of life

Assessment tool	RFA group			CAA group			Overall P value
	Preoperative	Postoperative	P value	Preoperative	Postoperative	P value	
VCSS	5.9 ± 1.2	0.9 ± 0.8	.017	5.8 ± 0.9	0.8 ± 0.6	.023	.721
AVVQ	19.7 ± 5.5	4.8 ± 1.5	.031	18.9 ± 5.8	4.9 ± 1.4	.038	.664

AVVQ, Aberdeen varicose vein questionnaire; CAA, cyanoacrylate ablation; RFA, radiofrequency ablation; VCSS, venous clinical severity score. Data presented as mean ± standard deviation.

although the same was not found on multivariate analysis. A preoperative CEAP class of ≥ 3 was a significant predictor of symptom recurrence. This finding has encouraged us to treat patients with positive Doppler ultrasound findings even at lower CEAP classes. We also found that bilateral limb disease, occupation requiring prolonged standing or low physical activity, a positive family history, and prior DVT were significant predictors of postoperative status. We found no significant differences in 5-year symptom-free survival rates between the RFA and CAA groups. The 60-month extension study of the VeClose trial reported that the 5-year freedom from recanalization in the CAA and RFA groups was 91.4% and 85.2%, respectively.²³ All these findings have demonstrated that preoperative patient characteristics are the primary determinant of the postoperative outcome. Other studies have reported similar results.¹⁵

The GSV occlusion rates and improvement in patient symptoms are both important for determining the effectiveness of an ablation technique. The VeClose extension study also reported that entire recanalization was not observed and that the patients with partial recanalization were asymptomatic. Similar to other studies, we found improvements in both VCSSs and AVVQ scores regardless of the treatment modality used.^{22,23,25,26} In the VeClose trial, patient satisfaction was 84.7% and 78.4% in the CAA and RFA groups at 36 months, respectively ($P = .30$).²² The VCSSs had declined by 75% in the CAA group and 72% in RFA group and the AVVQ scores had declined by 55% and 67% in the CAA and RFA groups, respectively.²³

Our study had several limitations, including its retrospective design and the lack of data for periprocedural pain. Our primary focus was to compare the closure rates for the two techniques, and we had not recorded some essential data such as the procedure time.

CONCLUSIONS

NTNT methods are believed to be the answer to the unwelcome effects of thermal, tumescent techniques. Ultrasound-guided foam sclerotherapy is one such NTNT method and, despite the possibly lower occlusion rate, has been shown to improve patients' quality of life.³⁰ Completed and ongoing studies have confirmed the noninferiority of CAA compared with thermal methods.^{9,23,25,26,31} RFA and CAA with a low viscosity NBCA provided comparable results at 5 years in our study. Perioperative considerations suggest that CAA might be the ideal treatment modality for most patients. Long-term outcomes and cost analyses from larger series are required to confirm our findings.

AUTHOR CONTRIBUTIONS

Conception and design: AD, FI
Analysis and interpretation: AD, FI
Data collection: FI

Writing the article: AD, FI

Critical revision of the article: AD, FI

Final approval of the article: AD, FI

Statistical analysis: FI

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AD and FI contributed equally to this article and share co-first authorship.

AD and FI contributed equally to this article and share co-senior authorship.

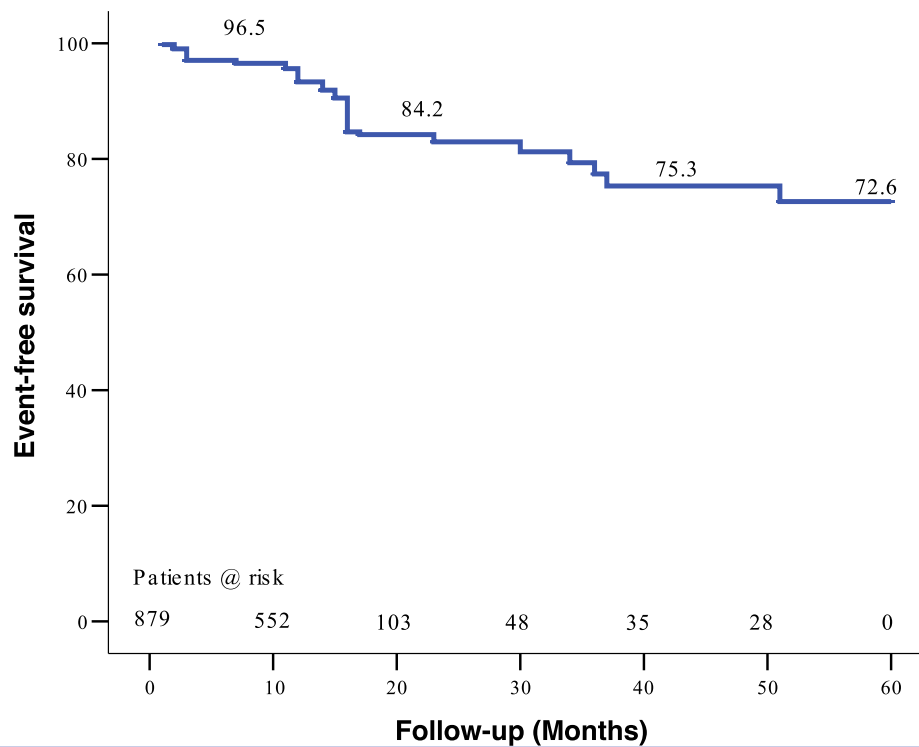
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Supplementary Fig (online only). Actuarial event-free survival rate for all patients. Standard error was never >10%.

Supplementary Table I (online only). Predictors of DVI on univariate and multivariate analyses

Predictive factor	Univariate <i>P</i> value	OR	95% CI	Multivariate <i>P</i> value
Sex (female vs male)	.008	27212	0.000-5.5E+42	.994
Preoperative DVI (yes vs no)	<.001	601.3	255.71-997.11	<.001
Occupation ^a	.001	46555	0.000-7.1E+49	.927

CI, Confidence interval; DVI, deep venous insufficiency; OR, odds ratio.

^aRequiring prolonged standing and/or low physical activity.

Supplementary Table II (online only). Predictors of postoperative perforator incompetence on univariate and multivariate analyses

Predictive factor	Univariate <i>P</i> value	OR	95% CI	Multivariate <i>P</i> value
Age (≥ 60 vs < 60 years)	<.001	9.012	8.223-11.103	<.001
Preoperative CEAP (≥ 3 vs < 3)	.002	1.119	1.119-3.005	.015
Occupation ^a (yes vs no)	<.001	0.105	0.027-0.204	<.001
Family history ^b (yes vs no)	.036	4.834	0.970-7.912	.087
Preoperative PI (yes vs no)	<.001	2.511	0.818-5.414	<.001

CEAP, Clinical, etiologic, anatomic, pathophysiologic; CI, confidence interval; OR, odds ratio; PI, perforator incompetence.

^aRequiring prolonged standing and/or low physical activity.

^bA family history of venous insufficiency.