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Early-Term Outcomes for Treatment of Saphenous Vein Insufficiency with N-Butyl Cyanoacrylate: A Novel, Non-Thermal, and Non-Tumescent Percutaneous Embolization Technique

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ABSTRACT

Background: The purpose of this study was to present early-term outcomes of VariClose® Vein Sealing System, which is a novel, non-thermal, and non-tumescent percutaneous embolization technique for treatment of saphenous vein insufficiency.

Methods: Between March 2014 and July 2015, 189 saphenous veins in 141 patients were treated with Variclose Vein Sealing System containing n-butyl cyanoacrylate. Pre-, intra-, post-procedural, and follow-up data of patients were collected and retrospectively reviewed.

Results: Mean age of patients was 42.5 ± 14.0 years, of which 53% were female. Technical success rate of intervention was 98.9%. Mean procedure time was 14.3 ± 7.5 minutes. Eighty-nine percent of patients (n = 126/141) were available at mean follow-up time of 6.7 months. Mean Venous Clinical Severity Score was significantly improved from 8.3 ± 2.2 at pre-procedure period to 3.3 ± 1.8 at follow-up. No complete recanalization was observed, but 2 patients were presented with partial recanalization during follow-up. The complete occlusion rate was 98.4%. No serious adverse event related to procedure was observed.

Conclusion: Variclose Vein Sealing System appears to be safe and effective in treatment of saphenous vein insufficiency. Further randomized studies with long-term outcomes are required for determining optimal treatment modality in patients with saphenous vein insufficiency.

INTRODUCTION

Varicose veins are as old as Hippocrates, and new treatment methods have become available in recent decades. For decades, open surgery was the gold standard of treating patients with venous disease in the lower limb attributable to saphenous vein insufficiency (SVI). However, minimally invasive techniques have changed the clinical landscape for varicose vein treatment tremendously [Van den Bremer 2010]. In 2001, Navarro and colleagues first reported on endovenous laser to eliminate insufficient great saphenous vein (GSV) segments, and this has been revolutionary for treatment of SVI [Navarro 2001]. After that, endovenous thermal ablation (EVTA) techniques became very popular and widely used for treatment of superficial venous insufficiency in many countries. EVTA by radiofrequency or laser ablation has been shown to be a safe and effective treatment method with high long-term venous occlusion rates. Nowadays, EVTA has become the most preferable therapy for superficial venous insufficiency [Gloviczki 2011; Van den Bos 2009]. However, these methods require the use of tumescent anesthesia and may cause adverse effects such as post-procedural pain, ecchymosis, hematoma, and sensory nerve damage [Almeida 2009].

In an effort to eliminate the requirement for tumescent anesthesia, while still maintaining the excellent results of EVTA, an alternative treatment method of ultrasound-guided foam sclerotherapy (UGFS) has been frequently used and its results evaluated. However, studies on UGFS reported relatively lower efficacy rates according to EVTA in different centers, with interim results of one randomized clinical trial suggesting a GSV occlusion rate of only 67.4% [Rabe 2008; Lattimer 2013]. Moreover, it has been reported that the rate of complications related to UGFS including inflammation, skin discoloration, visual disturbance, deep venous thrombosis (DVT), pulmonary embolism (PE), and stroke were higher than in EVTA [Ceulen 2007; Gillet 2009].

An endovenous embolization therapy for SVI using a tissue glue agent, cyanoacrylate (CA) adhesive, has recently been described, and two-year follow-up of the first human use was recently reported [Almeida 2015]. The advantages of this method are no requirement for tumescent anesthesia, thermal energy and post-procedure compression stockings, use of percutaneous access (with only local anesthesia), and short procedure time.

Actually, CA is not unknown to medical society, and it has been in use for peripheral embolization for many years [Pollak 2001]. Endovenously delivered CA immediately occludes the vein. It elicits a chronic granulomatous foreign body type inflammatory reaction, leading to segmental wall thickening,

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fibrosis, and venous closure [Almeida 2011].

A novel, non-thermal, and non-tumescent percutaneous embolization technique has been developed with use of a CA isoform, n-butyl cyanoacrylate (n-BCA), for treatment of SVI: Variclose Vein Sealing System (Biolas, Ankara, Turkey). The purpose of this study was to present early-term outcomes of Variclose Vein Sealing System in treatment of SVI.

MATERIALS AND METHODS

Between March 2014 and July 2015, 141 patients who underwent percutaneous endovenous embolization with n-BCA for SVI in our institution were included in this study. Pre-, intra-, post-procedural, and follow-up data of patients were collected and retrospectively reviewed. All patients were admitted to the outpatient clinic with symptoms of chronic venous insufficiency and/or varicosities, and duplex ultrasonography (DUS) was performed for diagnosis of all of them. The inclusion and exclusion criteria are listed in the . After clinical and DUS examination, 158 interventions to GSV and 33 interventions to small saphenous vein (SSV) were performed. In total, 189 embolizations were performed in 141 patients. All patients were informed in detail about the procedure and their consent forms were obtained before procedure. After the procedure, all patients were discharged without compression stockings on the same day after being followed for a few hours, with the requirement that if medical problem developed they must contact the hospital immediately.

Patients' clinical symptoms, physical examination findings, and CEAP classification were recorded. Venous Clinical Severity Score (VCSS) was calculated at both admission and follow-up. Furthermore, DUS was also performed on all patients at follow-up.

Procedural Technique

All procedures were performed in the operating room. Variclose Vein Sealing System was used for non-thermal endovenous ablation for all patients. Variclose Vein Sealing System contains n-BCA solution, and its delivery system in separate vials of 1 cc each, in sterile conditions within the Disposable VariClose kit. The kit consisted of 6F introducer, 0.035 inch guide wire, injector of 3 cc, injection gun, gun adapter, a 5F catheter with markers and 4F microcatheter (Figure 1). After providing adequate antisepsis of the leg, the saphenous vein was cannulated by ultrasound guided with local anesthesia at the entrance site. Then, the introducer was inserted into the saphenous vein and the catheter with marker was inserted 3 cm behind the saphenofemoral or saphenopopliteal junction (Figure 2). After the delivery system was prepared and the n-BCA solution was placed into the injection gun, it was attached to the microcatheter with spin-lock mechanism. The microcatheter was inserted through the 5F catheter, locked, and then brought into position. The tip of the microcatheter comes out by 3 cm inside from the 5F catheter and should be placed 3 cm below the saphenofemoral or saphenopopliteal junction. After the correct position of the microcatheter was confirmed by ultrasound guided, the solution was delivered into the vein. A few seconds before delivery of the solution into the vein, external compression was carried out proximal to the vein with the ultrasound probe, and then the proximal segment of the vein on which the procedure was to be performed was embolized. Priming of the microcatheter was performed with two small pulls of the trigger for 1 second. Then, the trigger of the gun was pressed for 5 seconds and the catheter pulled back by 2 cm/sec continuously and simultaneously. In the meantime, continuous pressure for 2 cm/sec was applied by ultrasound probe simultaneously following the catheter pullback. With each 5-second (or 10-cm) pull of the trigger of the gun, the catheter was simultaneously pulled back and pressure was applied by ultrasound probe. The procedure was continued until all vein segments were embolized. All venous systems were checked by ultrasonography after the procedures were completed. No adjunctive treatment such as phlebectomy or sclerotherapy to varicosities was performed at the time of procedure. Neither tumescent nor general anesthesia was applied in any of the patients.

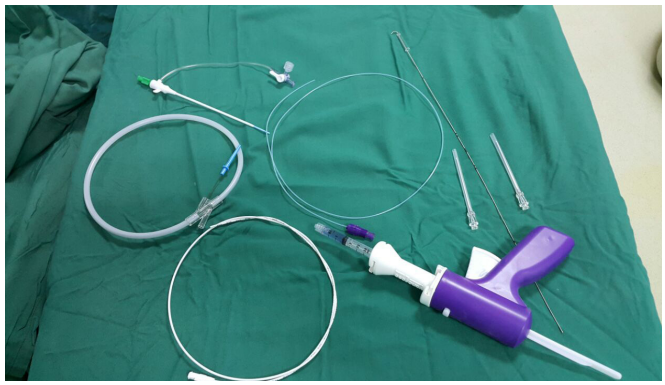

Figure 1. The components of the Variclose Vein Sealing System.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequency and percentages. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) program version 18.0 (SPSS, Chicago, IL, USA).

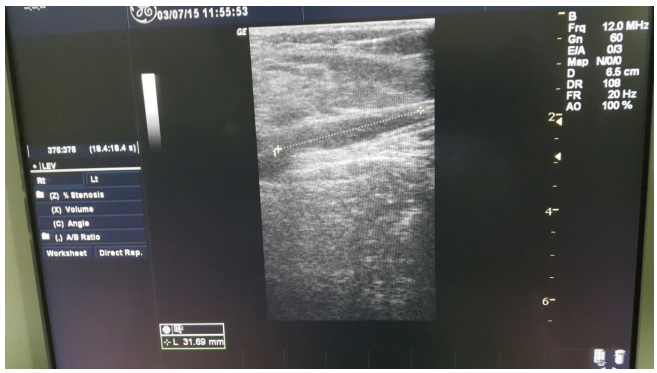

Figure 2. The distance between catheter tip and saphenofemoral junction (3 cm) is shown ultrasonographically.

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Table 1. Study Eligibility Criteria

Inclusion Criteria
1. Age ≥ 18 years and ≤ 80 years
2. Vein diameter at the GSV ≥ 5.5 mm and ≤ 15 mm & at the SSV ≥ 4 mm and ≤ 15 mm
3. Reflux time ≥ 2 second
4. CEAP classification between C1-C6
5. Patients who were sufficiently mentally healthy to consent to the intervention
Exclusion Criteria
1. Tortuous GSV or SSV
2. Symptomatic peripheral arterial disease history or an ABI index < 0.9
3. History of DVT or PE
4. Life expectancy < 2 years
5. Active thrombophlebitis in the deep or superficial veins
6. Significant femoral or popliteal venous insufficiency
7. Known sensitivity to cyanoacrylate adhesives
8. Aneurysm > 15 mm in the target vein
9. Previously treated GSV or SSV
10.Existence of malignancy
11. Pregnancy
12. Immobilization

GSV: Great saphenous vein, SSV: Small saphenous vein, DVT: Deep venous thrombosis, PE: Pulmonary embolism

RESULTS

Mean age of patients was 42.5 ± 14.0 years (range: 20-79), and 53% (n = 75) of them were female. The CEAP classification was C1 (6%, n = 8), C2 (22%, n = 32), C3 (43%, n = 62), C4 (21%, n = 30), C5 (6%, n = 9) and C6 (1%, n = 2). Mean preprocedure VCSS was 8.3 ± 2.2 (range: 5-19). Mean GSV diameter at the saphenofemoral junction was 7.6 ± 2.1 mm (range: 5.5-15), and mean SSV diameter at the saphenopopliteal junction was 7.0 ± 1.8 mm (range: 4.2-11). Most of the saphenous veins (79%) had continued reflux flow; the others had 2-6 second reflux with valsalva maneuver before the procedure.

A total of 191 interventions (158 to GSV and 33 to SSV) were planned; however, two interventions were unsuccessful due to shortening of vein diameter and vasospasm at the time of vein puncture. The technical success rate of intervention was 98.9%. Mean GSV and SSV treatment lengths were 30.2 ± 4.1 and 19.5 ± 3.8 cm, respectively. Mean delivered amount of n-BCA to GSV and SSV were 0.91 ± 0.12 and 0.58 ± 0.11 mL, respectively. Mean procedure time was 14.3 ± 7.5 minutes (range: 4-37). In the early post-procedural period, thrombophlebitis was observed in 6 (3%) patients, who were treated with oral non-steroidal anti-inflammatory drugs and/or antibiotics (two patients were treated with oral antibiotics, and one patient with parenteral antibiotics). Ecchymosis at the puncture area, with a size no greater than 10 cm, was observed in 4 (2%) patients. No hematoma, paresthesia, DVT, or PE were observed in any of the patients.

Follow-up was completed for 128 of the patients, but 15 patients were lost to follow-up. Additionally, two patients who underwent unsuccessful interventions were not considered for follow-up examination (reintervention was suggested for these patients, but they refused reintervention and were treated medically); in total, the results of a total of 126 patients were examined during follow-up. Mean follow-up time was 6.7 ± 4.1 months (range: 1-15). Post-procedure VCSS did not improve in only three patients; the rest were clinically better according to VCSS. Mean VCSS was significantly improved from 8.3 ± 2.2 at baseline to 3.3 ± 1.8 (range: 1-11) at follow-up. In DUS assessments, no complete recanalization was observed, but 2 patients presented with partial recanalization during follow-up. The complete occlusion rate was 98.4%. No adjunctive treatment of the target vein was required during follow-up period.

DISCUSSION

Chronic venous insufficiency (CVI) of the lower extremity is a common, progressive, disabling, and costly medical condition, which has a negative effect on patients' quality of life [Carradice 2011]. CVI affects more than 25 million adults in the United States and more than 6 million with more advanced venous disease [Beebe-Dimmer 2005]. In the most common manifestation of CVI, the valves in the GSV and other superficial veins transporting blood from the legs toward the heart are dysfunctional, leading to venous dilation and stasis, and causing symptoms and physical examination findings such as pain, swelling, chronic skin changes, spontaneous hemorrhage, and leg ulcers. CVI is found together with varicosities that originate from the GSV in almost 50% of cases, the SSV in 30%, and both veins in 20% [Labropoulos 1994].

Over the last decade, treatment of SVI and varicosis has undergone a substantial shift, and minimally invasive techniques, especially EVTA, have replaced traditional high ligation and stripping. Although EVTA procedures such as radiofrequency and laser have proven to be safe and effective, the use of these procedures come with some risks. The most known risk of EVTA is heat dissipation into the surrounding tissue and skin, which can cause superficial nerve damage and skin burns [Kerver 2012]. Therefore, tumescent anesthesia is required for protection from thermal damage, working as a heat sink. Occurrence of such complications with adequate tumescent anesthesia is rare; however, the use of tumescent anesthesia is an additional procedure requiring multiple needle injections that can be painful, and it also extends procedure time. The other rare risks of EVTA were described as device failures, DVT, PE, and peri-procedural death associated with PE [Malgor 2015].

The newer endovenous procedures for treatment of SVI without thermal energy and tumescent anesthesia have been developed as mechanochemical and chemical embolization procedures in recent years. These non-thermal procedures have potential benefits both for patient acceptability and decreased risk of nerve injury [McHugh 2014]. For this purpose, one of

these procedures is endovenous use of a CA adhesive chemical agent. Actually, CA is not a novel chemical agent in medicine. It has been used extensively in the medical field over the past 50 years, including for ophthalmic surgery, cosmetic procedures, dental applications, tissue adhesion, and hemostasis of acute bleeding. CA injection has specifically been used for endoscopic sclerotherapy for gastric variceal bleeding with high safety profiles reported in patients followed-up for 10 years [Akahoshi 2002]. CA-based compounds, especially n-BCA, have recently been introduced, at first experimentally, and then in clinical trials for treatment of SVI and varicosis. n-BCA is an adhesive liquid agent that, in contact with a solution containing anions, quickly polymerizes and becomes solid. Such processes cause inflammatory endothelial response and occlusion. No carcinogenic, mutagenic, or cytotoxic effect has been reported for n-BCA [Linfante 2007; Lawson 2013].

In our study, we used a proprietary formulation of n-BCA, namely Variclose Vein Sealing System. In this formulation, n-BCA was developed as a polymer structure that has been altered with addition of a monomer, synthesized by the producer company. Some minor alterations have been made in the chemical structure of this substance, and, as a result, its adhesive effect has been raised. Our early-term results in using Variclose Vein Sealing System for treatment of SVI were satisfactory, with lower complications rates when compared to other reports in the literature. The complete occlusion rate was 98.4% at a mean follow-up time of 6.7 months in our series. In a two-year follow-up study of first human use of CA adhesive in 38 patients for treatment of SVI, Almeida and colleagues have reported a 24-month occlusion rate of 92%. They have also reported an acceptable rates of side effects, the most frequent side effect being phlebitis in 16% of their patients [Almeida 2015]. In another recent study, a prospective multicenter study on CA embolization of GSV insufficiency that was conducted in 7 centers in 4 European countries, the authors have reported a 12-month follow-up results of 70 treated GSVs of 68 patients. Their 12-month complete occlusion rate was 93%, with mild and self-limited adverse events including post-procedure phlebitic reaction in 11% of patients [Proebstle 2015]. Morrison and colleagues recently performed a randomized trial comparing CA embolization and radiofrequency ablation for GSV insufficiency, and they have emphasized that CA embolization is not inferior to radiofrequency ablation for treatment of GSV insufficiency as a result of the study [Morrison 2015]. Furthermore, it was seen that VCSS was used as a common aspect of these recent studies for clinical assessment at follow-up, and mean post-procedure VCSS was improved in all of these studies, as in our series.

One significant difference between current literature and our study is the difference between phlebitis rates. Although closure rates seem as good as EVTA, phlebitis rates have a big gap. We believe that type of glue, polymerization time, glue viscosity, and application procedure can account for this difference. Continuous application of a low viscosity n-BCA with quick polymerization time without leaving any gaps inside of the vein treated with glue can decrease the phlebitis rate.

CA embolization was performed in 9 patients with C5 and in 2 patients with C6 in our series. In all 11 patients, post-procedure VCSS improved and complete occlusions were obtained at follow-up. Among C6 patients, the size of venous ulcer was decreased in one case, and the ulcer was fully regressed in another case at follow-up. Although not suitable for all patients with venous ulcer, CA embolization may also be beneficial in C5 and C6 patients.

No adjunctive treatment such as phlebectomy or sclerotherapy to branch varicosities was performed in our patients in the same session. Many surgeons routinely perform phlebectomy of branch varicosities in conjunction with endovenous ablation. They believe that complete removal of all varicosities at the initial procedure is the preferred treatment method for eradication of the reservoir, with better cosmetic results [Proebstle 2011]. With this in mind, it is not reasonable to perform a tumescentless embolization and use local anesthesia during the same procedure for performing the phlebectomies. Some authors are challenging these traditional treatment strategies and they suggest subsequent sclerotherapy after regression of varicosities [Welch 2006]. Almeida and colleagues have not performed adjunctive treatment for varicosities in the same session. In their series, the proportion of patients free from varicosities decreased somewhat at 24-month follow-up compared to 6-month follow-up. They have stated this may be due to progression of underlying disease. Therefore, this raises the question of whether concurrent phlebectomy or sclerotherapy of varicosities at the time of GSV closure is required [Almeida 2015]. In our series, we observed that 2 patients with partial recanalization were somehow connected to untreated relatively large branch varicosities with high blood flow or reflux. Perhaps the supplementary treatment of large branch varicosities at the time of procedure or early follow-up visit may raise the efficacy of index treatment.

To the best of our knowledge, this report is the first published clinical analysis of Variclose Vein Sealing System for treatment of SVI. Use of the Variclose Vein Sealing System enables treatment without either tumescent or general anesthesia. Moreover, wearing of compression stockings is not necessary after treatment. This means that patients may quickly return to work and operate vehicles. They may drive directly to work after the procedure and resume their general daily activities. They may also participate in sports more quickly. Furthermore, adverse events related to the procedure were acceptable, and no serious adverse event was observed in our series.

The major limitation of this study was the retrospective nature of the data collection of nonrandomized patients.

In conclusion, this study shows that Variclose Vein Sealing System is a novel, non-thermal, and non-tumescent endovenous embolization method that is safe and effective. Further randomized studies with long-term outcomes are required to determine the optimal treatment modality in patients with SVI.

REFERENCES

Akahoshi T, Hashizume M, Shimabukuro R, et al. 2002. Long-term results of endoscopic histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. Surgery 131(1 Suppl):S176-81.

Almeida JI, Kaufman J, Göckeritz O, et al. 2009. Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great

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saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol 20:752-9.

Almeida JI, Min RJ, Raabe R, McLean DJ, Madsen M. 2011. Cyanoacrylate adhesive for the closure of truncal veins: 60-day swine model results. Vasc Endovascular Surg 45:631-5.

Almeida JI, Javier JJ, Mackay EG, Bautista C, Cher DJ, Proebstle TM. 2015. Two-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. Phlebology 30:397-404.

Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. 2005. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol 15:175-84.

Carradice D, Mazari FA, Samuel N, Allgar V, Hatfield J, Chetter IC. 2011. Modelling the effect of venous disease on quality of life. Br J Surg 98:1089-98.

Ceulen RP, Bullens-Goessens YI, Pi-VAN DE Venne SJ, Nelemans PJ, Veraart JC, Sommer A. 2007. Outcomes and side effects of duplex-guided sclerotherapy in the treatment of great saphenous veins with 1% versus 3% polidocanol foam: results of a randomized controlled trial with 1-year follow-up. Dermatol Surg 33:276-81.

Gillet JL, Guedes JM, Guex JJ, et al. 2009. Side-effects and complications of foam sclerotherapy of the great and small saphenous veins: a controlled multicentre prospective study including 1,025 patients. Phlebology 24:131-8.

Gloviczki P, Comerota AJ, Dalsing MC, et al. 2011. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 53:2S-48S

Kerver AL, van der Ham AC, Theeuwes HP, et al. 2012. The surgical anatomy of the small saphenous vein and adjacent nerves in relation to endovenous thermal ablation. J Vasc Surg 56:181-8.

Labropoulos N, Leon M, Nicolaides AN, Giannoukas AD, Volteas N, Chan P. 1994. Superficial venous insufficiency: correlation of anatomic extent of reflux with clinical symptoms and signs. J Vasc Surg 20:953-8.

Lattimer CR, Kalodiki E, Azzam M, Makris GC, Somiayajulu S, Geroulakos G. 2013. Interim results on abolishing reflux alongside a randomized clinical trial on laser ablation with phlebectomies versus foam sclerotherapy. Int Angiol 32:394-403.

Lawson J, Gauw S, van Vlijmen C, et al. 2013. Sapheon: the solution? Phlebology 28(Suppl 1):2-9.

Malgor RD, Gasparis AP, Labropoulos N. 2015. Morbidity and mortality after thermal venous ablations. Int Angiol 35:57-61.

McHugh SM, Leahy AL. 2014. What next after thermal ablation for varicose veins: non-thermal ablation? Surgeon 12:237-8.

Morrison N, Gibson K, McEnroe S, et al. 2015. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg 61:985-94.

Navarro L, Min RJ, Boné C. 2001. Endovenous laser: a new minimally invasive method of treatment for varicose veins--preliminary observations using an 810 nm diode laser. Dermatol Surg 27:117-22.

Pollak JS, White RI Jr. 2001. The use of cyanoacrylate adhesives in peripheral embolization. J Vasc Interv Radiol 12:907-13.

Proebstle TM, Alm J, Göckeritz O, et al. 2011. 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 54:146-52.

Proebstle TM, Alm J, Dimitri S, et al. 2015. The European multicenter cohort study on cyanoacrylate embolization of refluxing great saphenous veins. J Vasc Surg: Venous and Lym Dis 3:2-7.

Rabe E, Otto J, Schliephake D, Pannier F. 2008. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. Eur J Vasc Endovasc Surg 35:238-45.

Van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. 2009. Endovenous therapies of lower extremity varicosities: a meta-analysis. J Vasc Surg 49:230-9.

Van den Bremer J, Moll FL. 2010. Historical overview of varicose vein surgery. Ann Vasc Surg 24:426-32.

Welch HJ. 2006. Endovenous ablation of the great saphenous vein may avert phlebectomy for branch varicose veins. J Vasc Surg 44:601-5.