Original article

Five-year follow-up of a randomized clinical trial comparing open surgery, foam sclerotherapy and endovenous laser ablation for great saphenous varicose veins

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Background: **New treatment methods have challenged open surgery as a treatment for great saphenous vein (GSV) insufficiency, the most common being ultrasound-guided foam sclerotherapy (UGFS) and endovenous laser ablation (EVLA). This study evaluated the long-term results of surgery, EVLA and UGFS in the treatment of GSV reflux.**

Methods: **Patients with symptomatic GSV reflux were randomized to undergo either open surgery, EVLA or UGFS. The main outcome measure was the occlusion rate of the GSV at 5 years after operation.**

Results: **The study included 196 patients treated during 2008–2010; of these, 166 (84·7 per cent) participated in the 5-year follow-up. At 5 years, the GSV occlusion rate was 96 (95 per cent c.i. 91 to 100) per cent in the open surgery group, 89 (82 to 98) per cent after EVLA and 51 (38 to 64) per cent after UGFS ($P < 0·001$). For patients who had received no additional treatment during follow-up, the occlusion rates were 96 per cent (46 of 48), 89 per cent (51 of 57) and 41 per cent (16 of 39) respectively. UGFS without further GSV treatment was successful in only 16 of 59 patients (27 per cent) at 5 years.**

Conclusion: **UGFS has significantly inferior occlusion rates compared with open surgery or EVLA, and results in additional treatments.**

Presented to the Annual Meeting of the European Society for Vascular Surgery, Porto, Portugal, September 2015, and to the Annual Operative Days of the Finnish Surgical Society and Finnish Society for Anaesthesiology, Helsinki, Finland, November 2015; published in abstract form as *Eur J Vasc Endovasc Surg* 2015; **50**: 398

Paper accepted 17 October 2017
Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10757

Introduction

Varicose veins affect up to 40 per cent of the adult population, causing symptoms that affect quality of life. The most common manifestations result from reflux of the great saphenous vein (GSV)[1]. There are many methods of treating GSV reflux: open surgery, foam sclerotherapy (UGFS), and endovenous catheter ablation using, for example, radiofrequency or laser energy. Although newer, less invasive endovenous techniques have replaced open surgery at many clinics, data on their long-term efficiency have so far been scarce[2–4]. An RCT[5] comparing these three methods in the treatment of unilateral GSV reflux was carried out at two university hospitals in Finland during 2008–2010. One year after the treatment, GSV reflux was significantly more common in the UGFS group than in the other two treatment groups. However, disease-specific quality of life was significantly better after 1 year compared with baseline in all treatment groups, with no significant difference between the groups. Similarly, varicose veins were absent in all groups at 1 year[5].

The aim of the present study was to report 5-year follow-up results of this RCT comparing open surgery, endovenous laser ablation (EVLA) and UGFS in the treatment of GSV reflux, in terms of both technical success and quality of life.

Methods

The study protocol, methods, and the 1-month and 1-year results have been described in detail previously[5]. Briefly, patients aged 20–70 years, with Clinical Etiologic Anatomic Pathophysiologic (CEAP) class C2–C4 varicose veins, and reflux in the GSV 5–10 mm in diameter were included. The final study population initially comprised

214 patients: 65 in the surgery group, 73 in the EVLA group and 76 in the UGFS group.

All patients from the RCT treated at Helsinki University Hospital were invited to attend a 5-year follow-up visit. The follow-up data for patients from Tampere University Hospital were not available. The Ethics Committee of Helsinki University Central Hospital approved this follow-up study. All patients had provided written informed consent for follow-up visits at the start of the trial.

Procedures

In the open surgery procedure, the GSV was stripped with a retrograde invagination technique, usually down to the upper calf. Most patients were treated under general anaesthesia. Tumescent liquid (450 ml Ringer's solution with 50 ml 1 per cent lidocaine with adrenaline (epinephrine)) was injected into the tunnel of the removed GSV as well as the hook phlebectomy sites after stripping. A class 2 compression stocking and bandages were applied for 48 h, with stocking use continued during the daytime for up to 2 weeks.

Tumescent anaesthesia was also used for EVLA; patients received a light sedative before (diazepam) and during (alfentanil, propofol) the procedure. In most patients, the surgeon inserted the laser catheter into the upper calf and, under ultrasound guidance, positioned the tip 1·5–2·0 cm below the saphenofemoral junction. A pulse mode with a 1·5-s impulse and 12 W of energy was used, aiming to apply 70 J/cm. Phlebectomies and after care were similar to those in the surgery group.

In the UGFS group, the surgeon cannulated the GSV, usually both at proximal thigh level and immediately below the knee. Sclerosant foam was prepared with a double-syringe technique using a sclerosant-to-air ratio of 1 : 2 using either 1 per cent polidocanol (Aetoxysclerol®; Kreussler, Wiesbaden, Germany) or 1 and 3 per cent sodium tetradecyl sulphate (Fibrovein™; STD Pharmaceutical Products, Hereford, UK). A compression stocking was applied afterwards to be worn continuously for 3 days, followed by daytime use for 11 days. All patients attended an appointment at 1 month and, if any reflux was observed on duplex imaging, a second treatment with foam was carried out, followed by a check-up 1 month later until the GSV was occluded.

Assessments

For this study, the patients were invited for examination 5 years after treatment. Assessments included a duplex ultrasound examination, clinical outcome evaluation, and disease-specific quality-of-life measurement using the Aberdeen Varicose Vein Severity Score (AVVSS)[6]. The closure of the GSV was classified as follows: absent/fully occluded, partial recanalization (at least 5 cm of compressible, patent GSV), or complete recanalization. Reflux was defined as a retrograde flow lasting more than 0·5 s after calf compression. The leg was also imaged for other refluxing veins, such as the anterior accessory saphenous vein (AASV). Neovascularization was defined by non-anatomical serpentine refluxing veins that entered the common femoral vein at the saphenofemoral junction. At both 1- and 5-year follow-up, if the patient had symptoms and either a recanalized GSV, a new refluxing venous segment such as the AASV, or neovascularization, they were assigned for additional treatment. The method of the additional treatment was decided by the treating physician.

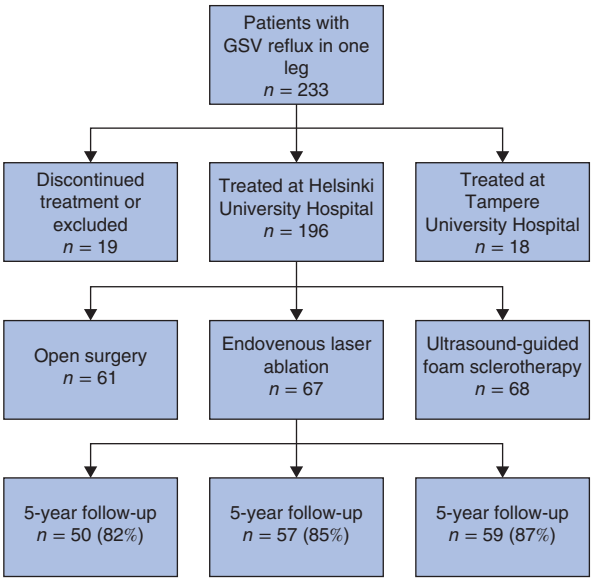


Fig. 1 Study flow chart. GSV, great saphenous vein

Statistical analysis

Data were evaluated by means of intention-to-treat analysis, but excluding missing data. The primary endpoint for the entire study, occlusion or absence of the GSV, was analysed in the overall study group and the three subgroups according to the initial size of the upper GSV.

Categorical values were compared using the χ^2 or Fisher's exact test, and numerical data using the Kruskal–Wallis test or linear regression, where applicable. Statistical analysis, including life-table analysis, was performed using SPSS® for Windows® version 22.0 (IBM, Armonk, New York, USA).

Table 1 Baseline characteristics of patients included in the follow-up study

	Open surgery ($n = 50$)	EVLA ($n = 57$)	UGFS ($n = 59$)	P†
Age (years)*	46·5(10·2)	47·7(13·4)	48·6(12·0)	0·601
BMI (kg/m^2)*	24·6(3·6)	25·4(3·5)	25·8(4·9)	0·379
Diameter of thigh GSV (mm)*	6·2(1·1)	6·3(1·1)	6·2(1·2)	0·515
CEAP class				0·085‡
C2	29	19	21	
C3	17	29	30	
C4	4	9	8	
Clinical disability score				0·882‡
0 (symptomless)	1	1	0	
1 (symptoms, no compression)	37	42	39	
2 (work only with compression)	12	14	20	
3 (not working even with compression)	0	0	0	
4 (hospital care)	0	0	0	
Side treated				
Right leg	21	30	21	
Left leg	29	27	38	

*Values are mean(s.d.). EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy; GSV, great saphenous vein; CEAP, Clinical Etiologic Anatomic Pathophysiologic. †Kruskal–Wallis test, except ‡χ^2 test.

Results

Of 196 patients initially treated at Helsinki University Hospital, 166 (84·7 per cent) attended for 5-year follow-up: 50 after open surgery, 57 after EVLA and 59 after UGFS (*Fig. 1*). This represented 77·6 per cent of the original study cohort (patients treated in Tampere were not included). Median follow-up was 5 years and 99 days (range 1485–2456 days) after treatment. Baseline clinical details in these patients were similar in all treatment groups (*Table 1*).

At 5 years, the GSV was completely occluded or absent in 48 of 50 patients in the surgery group (96 (95 per cent c.i. 91 to 100) per cent, 51 of 57 patients who had EVLA (89 (82 to 98) per cent) and in 30 of 59 patients who underwent UGFS (51 (38 to 64) per cent) (*Fig. 2*). The difference between the UGFS group and the EVLA or surgery group was statistically significant ($P < 0·001$).

At 5 years, there were no significant differences in the GSV occlusion rate according to initial sizes of the GSV, as analysed in three size groups (under 6, 6–9 and over 9 mm; $P = 0·290$).

The mean AVVSS score at 5 years was 8·7 (95 per cent c.i. 6·7 to 10·7) in the surgery group, 9·6 (6·4 to 12·8) in the EVLA group and 11·2 (8·5 to 14·0) in the UGFS group. Although the mean AVVSS was slightly higher after UGFS, the differences between the treatment groups were not statistically significant ($P = 0·636$).

By 5 years after surgery, a total of 22 patients had already received further treatment for the GSV: two (4 per cent) in the surgery group, none in the EVLA group and 20 (34 per cent) in the UGFS group. A subanalysis of non-assisted closure of the GSV (including only patients who had not received repeat treatment for the GSV) therefore included 48 patients in the surgery group, 57 in the EVLA group and 39 in the UGFS group.

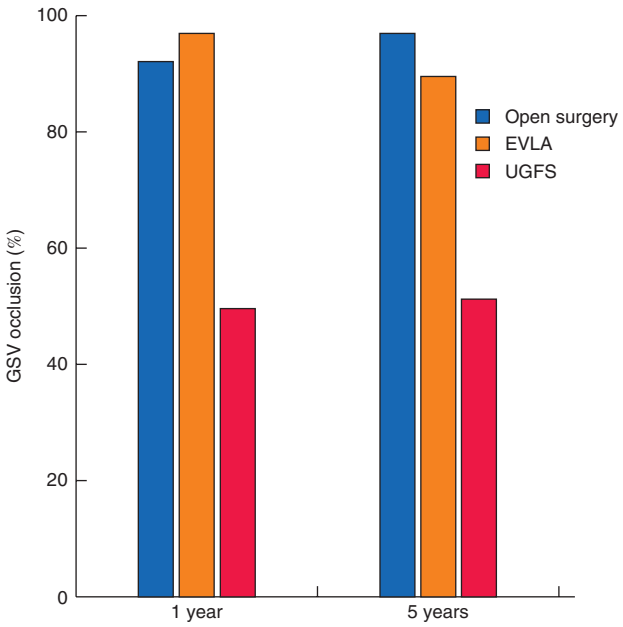
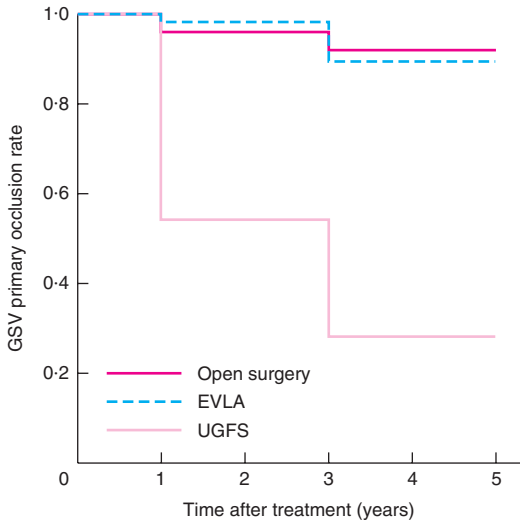


Fig. 2 Great saphenous vein (GSV) occlusion rates after treatment. EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy

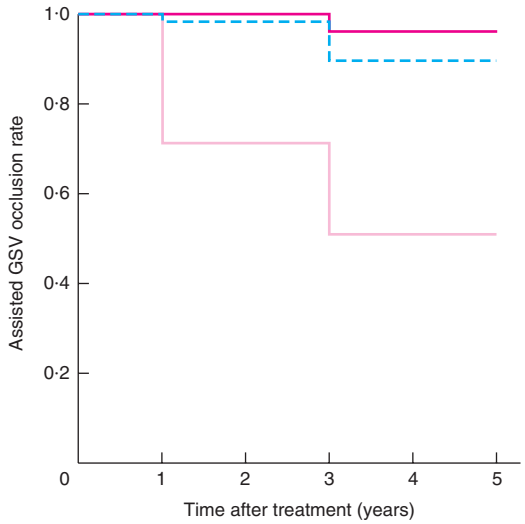
Non-assisted closure of the GSV occurred at 5 years in 46 of the 48 patients (96 per cent) in the surgery group, 51 of 57 (89 per cent) in the EVLA group and 16 of 39 (41 per cent) in the UGFS group. Primary and assisted occlusion rates are depicted in life tables (*Fig. 3*).



No. at risk

Open surgery	50	48	46
EVLA	57	56	51
UGFS	59	31	16

a Primary occlusion rate



No. at risk

Open surgery	50	48	48
EVLA	57	56	51
UGFS	59	42	30

b Assisted occlusion rate

Fig. 3 Life-table analysis of **a** primary occlusion rates and **b** assisted occlusion rates after treatment. EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy

Other outcomes

Of the 166 patients, 48 (28·9 per cent) either needed retreatment during follow-up or were assigned for retreatment at the 5-year visit. The odds of needing repeat treatment was 8·5 times higher for the UGFS group than for the EVLA group, and 1·6 times higher for the surgery group compared with the EVLA group.

Many patients in the UGFS group needed additional treatment for the GSV (*Table 2*). Two patients in the surgery group needed further treatment for the GSV; these represented incomplete stripping. In six patients in the EVLA group, either partial or full recanalization of the GSV occurred during follow-up. These patients had received a mean of 45·4 (range 20·7–66·1) J of laser energy per treated cm of GSV compared with 54·7 (19·7–85·4) J/cm among those with an occluded GSV at 5 years ($P = 0·150$). In general, there was no statistically significant correlation between the energy (J/cm) and 5-year outcomes of no reflux and absence of repeat treatments ($P = 0·143$). Of the six patients mentioned, three had partial recanalization of the GSV with no symptoms. The other three had complete recanalization, one of whom was symptomatic and received retreatment.

Two patients in the surgery group also had reflux originating from neovascularization in the groin. In the EVLA group, four patients received treatment for a refluxing AASV.

Altogether, 22 patients in the UGFS group who attended the 5-year follow-up had experienced either full or partial recanalization of the GSV at 1 year, but had no symptoms at that point. Three of the 16 patients with partial recanalization had already been retreated during follow-up and six were scheduled for EVLA at the 5-year follow-up visit, as the recanalization had become complete. One of the six patients with full recanalization had been treated

Table 2 Additional treatment in each study group

	Open surgery ($n = 50$)	EVLA ($n = 57$)	UGFS ($n = 59$)
Additional treatment scheduled or done	9	7	32
Repeat treatment for GSV	2	1	25
Additional treatment for anterior accessory saphenous vein	0	4	3
Additional treatment for neovascularized segments	2	0	0
Additional treatment for under-knee GSV or tributaries	5	2	4

EVLA, endovenous laser ablation; UGFS, ultrasound-guided foam sclerotherapy; GSV, great saphenous vein.

during follow-up and three were scheduled for treatment at the 5-year follow-up. The remaining patients were symptom-free.

There were no major complications related to the procedures, and long-term side-effects were rare. At the 5-year follow-up, two patients (4 per cent) in the open surgery group, one (2 per cent) in the EVLA group and two (4 per cent) in the UGFS group still had skin pigmentation. One patient treated with open surgery had a palpable lump under the skin. Paraesthesia was rare (1·8 per cent), with no differences between the treatment groups (1 in each group).

Discussion

Achieving good long-term freedom from recurrent superficial venous insufficiency after the treatment of GSV reflux is challenging. Less invasive techniques have replaced open surgery in many places owing to the faster recovery from the procedure.

There are several ways to categorize the success of varicose vein treatment. Patients who have partial or complete recanalization of the GSV after the initial treatment may remain asymptomatic and do not necessarily need additional treatment. However, here it seems that many did need retreatment. It was far more likely that patients treated initially with UGFS needed additional treatments, especially repeated treatment for the main GSV trunk. Therefore, although UGFS was initially the cheapest and most non-invasive treatment, it may have become more invasive and more expensive in the end.

At 1 year, the initial size of the GSV and its occlusion rate were correlated[5]. This was not observed at 5 years, probably because patients with a large, refluxing GSV had already been retreated at that point.

In all groups, the AVVSS scores at 1 year had improved significantly from baseline. This improvement was sustained during follow-up. The differences between the three groups in terms of quality of life at 5 years did not reach statistical significance, although there was a tendency towards higher scores indicating lower quality of life in the UGFS group.

The nature of additional treatments also reflected the technique used. As described by van Rij and colleagues[7], open surgery can lead to neovascularization from the groin. This occurs because angiogenesis is a natural part of wound healing, and can appear even after a 5-year interval[8]. In the present study, several patients in the open surgery group needed treatment for neovascular segments, but there were no patients with neovascularization after EVLA, similar to reports on EVLA from others[9].

When treating the GSV with EVLA, it is normal policy to leave the tip of the laser fiber 1–2 cm below the saphenofemoral junction. Therefore, any GSV tributaries that drain above that point are untreated. Frequently, the AASV remains open after EVLA. The AASV reflux that occurs after EVLA is thought to represent either neoreflux or failure to demonstrate the reflux during the pretreatment ultrasound examination. In the present study, the rate of AASV reflux after EVLA treatment was 7 per cent. The result supports the current practice of not treating the AASV if only GSV reflux is present[10].

There are studies suggesting that UGFS is a good option, although most of the data come from prospective series or retrospective analyses[11–14]. In many of these studies, the anatomical success rate (occlusion or absence of the GSV) is not very good, although patient satisfaction may be high. Recently published randomized trials comparing open surgery, EVLA and UGFS had quality of life or cost-effectiveness as endpoints, and evaluated UGFS to be a viable treatment option[15,16]. In these studies, however, follow-up was short.

It is argued that, in very skilled hands, UGFS might produce excellent results. In the present study, however, UGFS was administered by experienced vascular surgeons according to the best of their knowledge and ability, and repeated until the vein was seen to be fully occluded, making the procedure as effective as possible. However, after this, patients were not followed further. They later attended the 1-year follow-up visit, where reflux was observed in half of the patients. More frequent visits and an active refoaming policy in the presence of any reflux may have increased the occlusion rate in the long run, but would, again, have required more resources. Furthermore, as most of the patients were young, every visit would have meant a day off work. The present results reflect those seen in the real world. It is easier to standardize the EVLA procedure than UGFS, with EVLA having very repeatable results and a steep learning curve. Therefore, EVLA probably gives better results than UGFS in most clinical practice settings. EVLA can be administered as an outpatient, reducing the number of staff and materials required, thus making it cost-effective.

There are some limitations to the present study. Owing to the nature of the interventions, neither the patients nor the treating surgeons could be blinded to the intervention. The application of foam was not standardized, but optimal injection sites and sclerosants were used for each patient according to their anatomy. The assessor at the 5-year follow-up was not blinded to the type of treatment; in the majority of patients, the scarring pattern would have revealed it. Some crossover occurred but, as the main

results were analysed by intention to treat, this effect was minimized. Only patients who had unilateral GSV reflux on one side only participated in the study. This makes the results more reliable when considering the subjective experience of the patient.

Some patients were assigned for additional treatment at the 5-year follow-up visit. All of them had symptomatic recurrent venous disease. Many of these patients reported that they had already been about to obtain a referral for retreatment before they received the invitation to attend the follow-up visit. However, it could be argued that the rate of additional treatments was increased because of the follow-up visit, and some patients would not have sought additional treatment without it.

EVLA is a safe and effective means of treating GSV reflux, and the results are durable. It has a slightly lower rate of additional treatments needed afterwards than surgery. UGFS, in contrast, produced anatomical success without further GSV treatment at 5 years in only 27 per cent of the patients (16 of 59); patients in the UGFS group needed more repeat treatments. Primary GSV reflux is best treated with either open surgery or an endothermal ablation such as EVLA. UGFS should be considered as a valid treatment option for those with recurrent varicose veins or incompetent tributary veins, but its value in treating primary GSV reflux is low.

Acknowledgements

The authors thank all participating vascular surgeons, study nurses and staff at the vascular department and day surgery unit of Helsinki University Hospital for making this study possible. This article reports the results of a study preregistered with ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01298908).

Disclosure: The authors declare no conflict of interest.

References

1 Labropoulos N, Leon M, Nicolaides AN, Giannoukas AD, Volteas N, Chan P. Superficial venous insufficiency: correlation of anatomic extent of reflux with clinical symptoms and signs. *J Vasc Surg* 1994; **20**: 953–958.

2 Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Five-year results of a randomized clinical trial comparing endovenous laser ablation with cryostripping for great saphenous varicose veins. *Br J Surg* 2011; **98**: 1107–1111.

3 Rasmussen L, Lawaetz M, Bjoern L, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation and stripping of the great saphenous vein with clinical and duplex outcome after 5 years. *J Vasc Surg* 2013; **58**: 421–426.

4 van der Velden SK, Biemans AA, De Maeseneer MG, Kockaert MA, Cuypers PW, Hollestein LM *et al.* Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. *Br J Surg* 2015; **102**: 1184–1194.

5 Venermo M, Saarinen J, Eskelinen E, Vähäaho S, Saarinen E, Railo M *et al.*; Finnish Venous Study Collaborators. Randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. *Br J Surg* 2016; **103**: 1438–1444.

6 Garratt AM, Macdonald LM, Ruta DA, Russell IT, Buckingham JK, Krukowski ZH. Towards measurement of outcome for patients with varicose veins. *Qual Health Care* 1993; **2**: 5–10.

7 van Rij AM, Jones GT, Hill GB, Jiang P. Neovascularization and recurrent varicose veins: more histologic and ultrasound evidence. *J Vasc Surg* 2004; **40**: 296–302.

8 Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled trial of stripping the long saphenous vein. *J Vasc Surg* 2004; **40**: 634–639.

9 Theivacumar NS, Darwood R, Gough MJ. Neovascularisation and recurrence 2 years after varicose vein treatment for sapheno-femoral and great saphenous vein reflux: a comparison of surgery and endovenous laser ablation. *Eur J Vasc Endovasc Surg* 2009; **38**: 203–207.

10 Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AI, Gough MJ. Fate and clinical significance of saphenofemoral junction tributaries following endovenous laser ablation of great saphenous vein. *Br J Surg* 2007; **94**: 722–725.

11 Darvall KA, Bate GR, Bradbury AW. Patient-reported outcomes 5–8 years after ultrasound-guided foam sclerotherapy for varicose veins. *Br J Surg* 2014; **101**: 1098–1104.

12 Bradbury AW, Bate G, Pang K, Darvall KA, Adam DJ. Ultrasound-guided foam sclerotherapy is a safe and clinically effective treatment for superficial venous reflux. *J Vasc Surg* 2010; **52**: 939–945.

13 Chapman-Smith P, Browne A. Prospective five-year study of ultrasound-guided foam sclerotherapy in the treatment of great saphenous vein reflux. *Phlebology* 2009; **24**: 183–188.

14 Myers KA, Jolley D. Outcome of endovenous laser therapy for saphenous reflux and varicose veins: medium-term results assessed by ultrasound surveillance. *Eur J Vasc Endovasc Surg* 2009; **37**: 239–245.

15 Biemans AA, Kockaert M, Akkersdijk GP, van den Bos RR, de Maeseneer MG, Cuypers P *et al.* Comparing endovenous laser ablation, foam sclerotherapy, and conventional surgery for great saphenous varicose veins. *J Vasc Surg* 2013; **58**: 727–734.e1.

16 Brittenden J, Cotton SC, Elders A, Ramsay CR, Norrie J, Burr J *et al.* A randomized trial comparing treatments for varicose veins. *N Engl J Med* 2014; **371**: 1218–1227.