Article:
Carroll, C. orcid.org/0000-0002-6361-6182, Hummel, S., Leaviss, J. orcid.org/0000-0002-5632-6021 et al. (4 more authors) (2014) Systematic review, network meta-analysis and exploratory cost-effectiveness model of randomized trials of minimally invasive techniques versus surgery for varicose veins. British Journal of Surgery , 101 (9). pp. 1040-1052. ISSN 0007-1323

https://doi.org/10.1002/bjs.9566

Title:

Minimally invasive techniques versus surgery for management of varicose veins: A systematic review and network meta-analysis of randomised clinical trials and exploratory cost-effectiveness model

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Funding:

This report was commissioned by the NIHR HTA Programme as project number 10/29/01.

Type of publication:

Review

Keywords:

Systematic review, cost-effectiveness, varicose veins, health technology assessment

Abstract

Background:

A Health Technology Assessment was conducted to evaluate the relative clinical and cost-effectiveness of minimally invasive techniques (foam sclerotherapy (FS), endovenous laser ablation (EVLA) and radiofrequency ablation (RFA)) for managing varicose veins, in comparison with traditional surgery.

Methods:

A systematic review of randomised controlled trials (RCTs) to assess the effectiveness of minimally invasive techniques compared with other treatments, principally surgical stripping, in terms of recurrence of varicose veins, Venous Clinical Severity Score (VCSS), pain and quality of life. Network meta-analysis and exploratory cost-effectiveness modelling were performed.

Results:

The literature search conducted in July 2011 identified 1453 unique citations: 34 RCTs (54 papers) satisfied the criteria for effectiveness review. Differences between treatments were negligible in terms of clinical outcomes, so the treatment with the lowest cost appears to be most cost-effective. Total FS costs were estimated to be lowest and it was marginally more effective than surgery. However, relative effectiveness was sensitive to the model time horizon. Threshold analysis indicated that EVLA and RFA might be considered cost-effective if their costs are similar to surgery. These findings are subject to various uncertainties, including the risk of bias present in the evidence base and variation in reported costs.

Conclusion:

This assessment of the currently available evidence suggests there is little to choose between surgery and the minimally invasive techniques in terms of efficacy or safety, so the relative

costs of the treatments becomes one of the deciding factors. High quality RCT evidence is needed to verify and further inform these findings.

Introduction

The prevalence of varicose veins in the UK has been reported to be between 20-40% in adults. The NHS performed over 33,000 surgical procedures in 2010-11 to treat varicose veins. However, the perceived low priority of varicose veins in economically straitened times may explain the recent reductions in varicose vein activity in England and Wales.[1]. Conventional surgery (ligation and stripping) remains the most frequently performed procedure in the National Health Service (NHS)[2;3] although there are regional variations in the type of procedures performed.[2] However, ligation and stripping has been associated with a range of adverse effects such as wound infection, haematoma, lymph leaks, pain, scarring, nerve injury, Deep Vein Thrombosis (DVT) and long post-operative recovery.[4-7] Conventional non-foam sclerotherapy, is considered faster but less effective than surgical stripping (hereafter, "surgery").[8]

The clinical signs and symptoms of venous disease may be classified using the CEAP classification: Clinical status; Etiology; Anatomy; and Pathophysiology.[9-11] This ranges from C0 (no signs of venous disease) to C6 (active venous ulcer). C2 indicates varicose veins. The degree of severity of pain and other clinical signs or symptoms can be measured according to the Venous Clinical Severity Score (VCSS).[12;13] The VCSS may be used to gauge clinical severity before and after intervention, i.e. to measure the efficacy of an intervention. The higher the score, the worse the disease severity. The presence of reflux is identified principally by duplex ultrasound (DUS). The criteria usually taken as indicating pathological reflux are the presence of venous flow reversal for >0.5 to 1.0 second with proximal compression, the Valsalva manoeuvre, or distal compression and release.[14]

The principal outcomes associated with treatment for varicose veins are symptom relief and symptom severity, recurrence of varicosities, as well as the occurrence of new varicosities in

the same limb, and retreatment. Reported recurrence rates vary widely depending on the nature of the surgical technique performed and method of assessment. For conventional stripping and ligation surgery, two-year recurrence rates of up to 33% have been reported[15;16], rising to 41% for 5 years and to up to 70% at over 10 years.[17;18] Surgical procedures for recurrence can therefore place considerable demand on the health services. Other outcomes of interest are health-related quality of life (HRQoL), patient treatment satisfaction, and the occurrence of related post-operative complications.

New minimally invasive treatments offer alternative methods of ablating incompetent veins, particularly the Greater Saphenous Vein. These treatments typically involve use of laser (endovenous laser ablation, EVLA)[19], radiofrequency probe (RFA)[20] or foam sclerosant (FS).[21] They are increasingly widely used and might offer potential benefits such as faster recovery, reduced complications, fewer physical limitations and increased HRQoL. In terms of active intervention, recent Guidance from the National Institute for Health and Care Excellence (NICE) recommends the use of EVLA or RFA; if this is considered ”unsuitable”, then FS should be used, and, if this technique is deemed ”unsuitable”, then surgery should be used.[22] The study reported here was funded as a Health Technology Assessment report by the National Institute of Health Research (NIHR); the full detailed report is available elsewhere.[23] It aimed to evaluate the clinical and cost effectiveness of the different minimally invasive methods of managing varicose veins compared with conventional surgery.

Methods

Clinical effectiveness

Inclusion and exclusion criteria

To be included in the review, a study had to be a randomised controlled trial (RCT) of adults aged 16 years or more who were being treated specifically for varicose veins and who received one of the following interventions (EVLA, RFA or FS). The comparator could be any of these treatments, surgery or conservative management. Outcomes included failure of the procedure, i.e. the procedure was incomplete; or occlusion or obliteration was not achieved or was not sustained for more than one month; technical recurrence (as distinct from initial episode), i.e. the presence of reflux, recanalisation or new varicose veins in a treated limb, diagnosed by duplex ultrasound scanning (DUS); Venous Clinical Severity Score

(VCSS); pain; time to return to work or normal activity; and post-operative complications (adverse events). Trials comparing different forms of the same intervention were excluded. Only the meta-analysed outcomes of technical recurrence, VCSS and pain are reported in this article.

Search strategy and study selection

A systematic review of the literature and (network) meta-analysis was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[24] A comprehensive search was undertaken to identify systematically clinical effectiveness literature comparing different methods for the management of varicose veins. The search involved combining terms for the population (varicose veins) with terms for the interventions of interest, i.e. the minimally invasive techniques. The full search strategy is available in the full report.[23] All searches were performed in July 2011. Eleven electronic databases were searched from inception for published and unpublished research evidence: MEDLINE, EMBASE, CINAHL, The Cochrane Library, Biological Abstracts, Science and Social Science Citation Indices, Conference Proceedings Citation Index- Science (CPCI-S), UK Clinical Trials Research Network (UKCRN), Current Controlled Trials and Clinical Trials.gov. All citations were imported into reference management software and titles and abstracts of all unique citations were screened independently by two reviewers using the inclusion criteria outlined below. Disagreements or queries were resolved by consensus or with reference to a third team member where necessary. The full papers of all potentially relevant citations were assessed for inclusion and reference-tracking of all included studies and relevant reviews was performed to identify additional, relevant studies not retrieved by the search of electronic databases.

Data extraction, critical appraisal and synthesis

Data extraction was performed by one reviewer into a standardised form and independently checked for accuracy by a second reviewer. Discrepancies were resolved by discussion. Critical appraisal of included trials was performed by one reviewer, using appropriate criteria adapted from a published checklist for surgical interventions, and independently checked for accuracy by a second. Discrepancies were resolved by discussion between reviewers. Blinding of patients and outcome assessors were not retained as criteria because the techniques generally did not permit such blinding, so the risk of detection bias was inherently high in all studies.

Methods of data synthesis

Technical recurrence, VCSS and pain score data were tabulated and, where data were appropriate, included studies were combined in a random-effects network meta-analysis, which allows for heterogeneity in treatment effects across studies. Randomisation and analysis in the primary studies was described as being by patient or by limb when patients were unilateral; when patients were bilateral, randomisation was by limb. Data were therefore all per limb or per patient; no data were per procedure (i.e. there were no data where multiple procedures were conducted on the same limb). The analysis was conducted using Markov chain Monte Carlo (MCMC) simulation implemented in the WinBUGS and OpenBugs software packages.[25;26] The principal analysis compared the hazard of having technical recurrence when treating with EVLA, RFA and FS, relative to the common comparator of surgery using a complimentary log-log link function assuming that the underlying survivor functions follow Weibull distributions with separate shape and scale parameters to allow for the possibility of non-proportional hazards; a summary of the treatment effects is presented for 6 months, 1 year and 2 years. For VCSS and pain scores, the statistical model assumed a normal distribution for the observed sample means. Convergence of the models to their posterior distributions was assessed using the Brooks-Gelman-Rubin convergence statistic.[27] Convergence occurred after 200,000 iterations for technical recurrence, after 10,000 iterations for VCSS and after 30,000 iterations for pain. Full details of the analysis are given elsewhere.[23]

Cost-effectiveness

Model Overview

The model was developed as a discrete event simulation (DES) model in Simul8® to simulate the experience of patients undergoing treatment for varicose veins. A DES model was chosen to allow non-constant hazard in the time to treatment failure/technical recurrence. This method also obviates the need for arbitrary time cycles. The baseline model had a perspective of ten years, chosen as a reasonable time over which to extrapolate the time to failure data. Costs were reported in 2011-12 British Pound Sterling; quality adjusted life years (QALYs) were used as the measure of effectiveness. The analysis took the perspective of the UK NHS and personal social services. All costs and benefits are discounted at a rate of 3.5%, as

recommended NICE.[28] Both probabilistic (PSA) and deterministic sensitivity analysis were undertaken.

The model structure

The model structure is illustrated in **Figure 1**. Ovals represent events (numbered 1 to 3) and oblongs health states (A to D). Treatments included in the model are surgery, FS, EVLA, and RFA (Event 1). Costs and a loss of utility from the short term adverse effects of treatment are assigned according to the treatment. Treatment may result in technical immediate (anatomical) success (states A and B) or failure (states C and D). If a failure, it is assumed that all patients will have further treatment with foam until technical success is achieved (Event 2). Patients with a successful clinical outcome nevertheless still have a probability of remaining symptomatic (state B). Thus initial treatment may result in one of two health states (A,B) based on the presence or absence of symptoms. Outcomes of varicose vein procedures are complex. Several disease-specific quality of life measures have been developed for varicose veins in recognition of the fact that whilst symptom relief is associated with clinical or anatomical outcomes, these are poor predictors of operative success from the patient's perspective.[29;30] For example, in a study of FS no correlation was found between changes in the Aberdeen Varicose Veins Questionnaire (AVVQ), a patient-reported measure of outcomes and quality-of-life, and venous refill times.[29] Also, Merchant reports a high proportion of patients experiencing symptom improvement despite anatomical failure following RFA (70%-80%, compared to 85%-94% in limbs with anatomical success).[30] In the model it was therefore not assumed that technical failure equates to the patient being symptomatic. Instead patients with technically successful and technically failed procedures have differing probabilities of being asymptomatic, with differing utility values attached to symptomatic and asymptomatic states. Patients may die at any time of all-cause mortality.

Adverse events, other than post-operative pain, are not included in the model because most adverse events of treatment, such as infection, haematoma, paraesthesia and phlebitis are relatively mild, of short duration and require no treatment. An exception is DVT, which can occasionally lead to death. However, the effectiveness review showed that DVT following treatment for varicose veins is very rare and so any possible effects on the model results were estimated to be negligible.

Figure 1 here: Model structure

Model Parameters

Uncertainty about parameters representing disease recurrence data and post-operative pain were sourced from the network meta-analysis (see Results). The proportion of patients requiring treatment for initial failure (treatment failure by one month) was determined from the time to failure distribution and top-up treatments for residual side branches and accessory saphenous veins estimated from additional meta-analysis of data from studies included in the effectiveness review. Both were assumed to be treated with FS.Studies varied in their use of phlebectomy concomitant with the primary procedure. In the model the initial procedure includes a proportion that would be undergoing concomitant phlebectomy in keeping with the trial evidence. Most used FS rather than phlebectomy for residual varicosities requiring secondary procedures unless there was recurrent incompetence. It was therefore assumed that 60% of late (after one month) retreatments were surgical procedures (stripping) and 40% FS. The proportion of patients asymptomatic following a technically failed or successful procedure was taken from the literature.[30;31] Procedure costs were derived from UK studies identified in a systematic search for economic studies of included treatments. However, only the cost of surgery was available from more than one study and was quite variable, ranging from £660 to £1,420 at 2011/12 prices.[32-34] The cost for surgery was therefore taken from National Reference costs, but these do not differentiate between the other treatment methods.[35] The cost of other treatments relative to surgery was published only in a small number of studies, so this information had to be used to calculate their cost, as shown **Figure 2**. The costs of EVLA were estimated from those for RFA, based on additional equipment costs. To address variation in treatment costs a threshold analysis was performed to determine the cost at which the minimally invasive treatments might be considered cost-effective. Resource use (GP and outpatient visits, duplex scan) associated with retreatment were estimated and costed using standard sources.[35;36]

To derive an estimate of the utility associated with symptomatic varicose veins a meta-analysis was undertaken of all studies reporting baseline (pre-treatment) EQ-5D in this population.[34;37-41] Six relevant studies were identified with 1177 unique patients. Age-independent estimates were calculated by dividing the reported values by the population average utility for the mean study population ages.[42] This gave a utility value of 0.88 (se 0.009) for patients with symptomatic varicose veins. Asymptomatic patients are assumed to have the same utility as the general population of their age, so the state utility value is one. In the model age-specific utility is calculated by multiplying the state utility by the age-dependent utility. Loss of utility associated with post-operative pain was estimated from a

single study reporting both.[43] The reduction in EQ-5D utility for each absolute 1% increase in VAS pain score was 0.0026. All parameter values are reported in Supplementary Data Table S1 except time to recurrence (see **Figure 8** in Results section).

Figure 2 here: Initial procedure costs estimated relative to surgery costs

Results

Clinical effectiveness review

Included studies

The searches identified 1453 unique citations. See the PRISMA flowchart below (**Figure 3**). Eleven citations represented relevant ongoing trials and 51 citations, representing 31 different studies [32;41;43-71], provided data used in the network meta-analyses. Study characteristics for these trials are shown in Table S2 (supplementary information). Fourteen trials evaluated EVLA against surgery, RFA or FS; thirteen trials compared RFA with surgery, EVLA, FS or other comparators; and thirteen trials evaluated FS, principally comparing it with conventional surgery. One trial had arms comparing all three minimally invasive techniques.[56] No trial included conservative management as a comparator. The principal, common comparator was surgery, i.e. ligation and stripping.

3873 participants were reported as randomised across all trials. The number of randomised participants in a single trial ranged from 28[45] to 710.[48] The mean age of participants ranged from 33to 54 years.[52;53;72] There was a majority of female participants in every trial; the percentage of female participants ranged from 54%[52] to 95%.[54] In all trials participants were required to have varicose veins diagnosed by duplex scanning and categorised according to the CEAP score. The vast majority of participants in any trial were C2 on the CEAP score (varicose veins), except for three trials, where the majority were C3[53], C4[49] or C5.[55] The UK was the single most frequent location (12 trials); the remainder were conducted in centres across thirteen other different countries.

Quality of included studies

The methodological quality assessment of each included study is summarised in Table S3 (supplementary information). The majority of the trials used in the network meta-analyses (e.g. those reporting technical recurrence data for EVLA versus surgery or EVLA versus RFA etc.) were at risk of either selection or attrition bias due to inadequate randomisation, allocation concealment or intention-to-treat analysis. Only four of the included trials actually reported that surgeons were sufficiently experienced across arms in the various procedures, thus reducing the likelihood of bias resulting from performance of the various techniques.[61;63;65;73]

Recurrence

The principal outcome reported by trials was technical recurrence, as defined above. Data were available from 23 trials at various follow-up times.[41;43-49;51-56;61;72-77] The results suggested that there was mild heterogeneity between studies in the shape parameter (0.17; 95% CrI: 0.01, 0.45) but that there was mild to moderate heterogeneity between studies in the scale parameter (0.26; 95% CrI: 0.02, 0.91). EVLA exhibited the lowest rates of technical recurrence relative to surgery, although there was some evidence that this benefit decreases over time (2 Year HR, 0.84; 95% CrI: 0.44, 1.81) (see **Figure 4**). RFA was associated with a small and relatively constant lower rate of technical recurrence over time compared with surgery (2 Year HR, 0.94; 95% CrI**:** 0.42, 2.51). FS was worse than surgery over the first year, although there was a small benefit after two years (2 Year HR, 0.92; 95% CrI**:** 0.43, 1.60). In each case there was considerable uncertainty about which intervention was the most beneficial.

Figure 4 here: Technical recurrence

Venous Clinical Severity Score (VCSS)

Thirteen studies met the inclusion/exclusion criteria for VCSS as an outcome, although 1 year data was available from only 6 studies.[43;46;57;63;66;78] The between study standard deviation (SD) was estimated to be 0.22, which is indicative of mild to moderate heterogeneity in treatment effect between studies (95% CrI: 0.01, 1.79). The VCSS for both FS and EVLA were lower than for surgery, i.e. patients and clinicians reported fewer clinical symptoms for these treatments compared to surgery. (See **Figure 5**).

Figure 5 here: VCSS

Pain score

Eleven trials reported measuring pain using a form of visual analogue scale (1-10 or 1-100) for a period between three and 14 days post-operation and were included in the network meta-analysis.[41;45;53;56-59;61;63;64;79] The between study standard deviation was estimated to be 0.48; (95% CrI: 0.06, 1.12), which is indicative of mild to moderate heterogeneity in treatment effect between studies. The interventions that exhibited the lowest pain scores compared to surgery were RFA (mean difference, -1.26 95% CrI: -1.95, -0.61) and FS (mean difference, -0.80 95% CrI: -1.93, 0.30). (See **Figure 6**)

Figure 6 here: Pain scores

Adverse events

In general, serious adverse events, such as DVT or pulmonary embolism (PE) were rare. Eleven studies reported on these outcomes but only five studies reported that any such complication actually occurred.[46;48;56;63;80] The three trials reporting the highest numbers of these adverse events, i.e. Wright[78], Rasmussen et al., 2011[87] and Shadid et al.,[125], also had the largest sample sizes of all included studies in the review[48;56;80], with Wright et al[48] reporting a substantially higher rate than any other study. However, this disproportionate rate can be explained by the intervention. The "VARISOLVE®" technique (BTG, London, UK) applied in this trial was new and the amount of foam used was altered part way through the trial because of the high DVT rate: the initial amount of foam (60mL) was reduced to 30mL. No DVT was reported for the 95 participants who subsequently received this lower dose.

Summary of effectiveness

The analysis of the technical recurrence data suggested that the benefit of treatment with EVLA and FS varied over time. In particular, the early benefit associated with EVLA relative to surgery was less at 2 years than at 6 months. However, the results were inconclusive in determining which intervention was the most effective. The analysis of the VCSS data suggested that FS was the most effective intervention. The analysis of the pain score data suggested that RFA was the most effective treatment.

Cost-effectiveness

The results of the PSA analysis, with costs and QALYs discounted at a rate of 3.5%, are shown in **Figure 7**. Although there is an element of retreatment, the total costs of treatment are primarily comprised of the initial treatment cost, with RFA the most expensive procedure and FS the least costly option. All of the minimally invasive treatments result in more QALYs compared to surgery at 10 years, but the QALY differences between surgery, EVLA and RFA are negligible: equivalent to less than a day in full health for EVLA compared to surgery.

Figure 7 here: Results of the discounted PSA economic analysis

Foam is less costly than surgery and marginally more effective, and can thus be said to dominate surgery. The probability of it being the most cost-effective treatment is above 90% for willingness to pay thresholds in the range £20,000 to £50,000. The Incremental Cost Effectiveness Ratios (ICERs) for EVLA and RFA, in comparison to surgical stripping, show they are not cost-effective at usually accepted levels.[28]

The full results of the univariate sensitivity analysis are reported elsewhere.[23] The results were not sensitive to uncertainty associated with most parameters, with the exception of the disutility associated with post-operative treatment, and the model time horizon. The results for FS compared to surgery were potentially sensitive to disutility associated with treatment, a parameter derived from the network meta-analysis of reported pain at approximately 10 days (see **Figure 6**). By 10 days post-operative pain has already subsided, and therefore the analysis may not fully reflect differences between the treatments. Also the relationship between post-operative pain and utility was based on limited data.[43]

The model time horizon has the potential to affect results due to differences between the treatments in post-operative pain and recurrence rates. (See **Figures 4** and **8**) For EVLA and RFA the incremental QALYs are greater and the costs lower with increasing timespan as their failure rates are lower than for surgery (Hazard ratio [HR] at one year 0.77 for EVLA, 0.93 for RFA), so the ICERs are lower the longer the model time horizon, but even run for a lifetime the ICERs do not approach £30,000. RFA results in less post-operative pain than EVLA, so RFA results in more QALYs at two years compared to EVLA, but by 10 years EVLA has overtaken RFA due to lower failure rates. For FS the picture is more complex. The

pain associated with treatment is lower than for surgery, resulting initially in higher QALYs. However the rate of failure is slightly higher in the first few years compared to surgery (HR foam 1.02 at one year) potentially resulting in fewer QALYs for intermediate model timespans. In the long term (between 10 years and life) foam has a lower failure rate than surgery and leads to a small QALY gain.

Figure 8 here: Probability of technical recurrence by intervention (mean)

Summary of cost-effectiveness

Differences between treatments are negligible in terms of clinical outcomes, so the treatment with the lowest cost appears to be most cost-effective. Our central estimate is that total FS costs are the lowest and it is marginally more effective than surgical stripping (+0.0015 QALYs), with a probability of being the most cost-effective treatment above 90% for willingness-to-pay thresholds in the range £20,000–50,000. This result is, however, sensitive to the model time horizon (i.e. cost-effectiveness is reduced in the shorter term because of the early failure rates for this technique). EVLA and RFA both cost more than surgery, and with very little difference in QALYs they cannot be considered cost-effective at the usual threshold of £20,000–30,000, a result that is robust to parameter variation and model time horizon. There is considerable uncertainty in the cost differences between treatments arising from different reported costs of the procedures, and in fact these are likely to vary with setting, and may also vary over time. Threshold analysis showed that the additional costs of EVLA and RFA would have to be not more than £50 and £24 more than surgery, respectively, to be considered cost-effective at a threshold of £20,000.[23]

Discussion

This assessment of the evidence published up to August 2011 suggests there is little to choose between the minimally invasive techniques in terms of efficacy or cost, and each offers a viable, clinically effective alternative to stripping. FS might offer the most cost-effective alternative to stripping, within certain time parameters, although there is some uncertainty over the longer-term benefits.[81] EVLA and RFA both cost more than surgery, and with very little difference in QALYs they cannot be considered cost-effective at the usual threshold of

£20,000 - £30,000.[28] However, there was limited cost data for the procedures apart from surgery, where reported costs were quite variable. Cost differences between treatments are therefore highly uncertain. EVLA and RFA were marginally more effective than surgery so if their costs were similar to surgery they would be considered cost-effective. In view of the small absolute differences in costs and outcomes between the techniques, other issues of importance to patients, such as the less invasive nature of some options, the opportunity to avoid larger scars and general anaesthesia may be important in the choice of procedure. Furthermore, if wider social benefits, such as speed of recovery and return to work, were to be considered in costs, then the minimally invasive techniques might demonstrate further benefits over surgery, the majority of studies evaluating time to return to work or normal activity report a significant reduction for the minimally invasive techniques compared to surgical stripping.[23]

All of the effectiveness analyses presented here used only technical rather than symptomatic recurrence data, so the true proportion of treated individuals who are likely to present with symptoms of recurrence requiring retreatment is not certain. The rates of technical recurrence reported here are therefore higher than those encountered in clinical practice because non-symptomatic patients would not present, even if they were experiencing technical recurrence. The findings on initial failure and retreatment, symptomatic recurrence and retreatment for recurrence, given in the full report[23], are affected by a high degree of uncertainty due to the relative infrequency with which such data were reported, as well as the limitations of the primary studies' reporting of these data. Based on projections from trial data the long-term risk of a technical recurrence is less for all the minimally invasive treatments compared with surgery, although the time to treatment failure curves are quite similar.

The cost-effectiveness model shows that any differences in benefits (QALYs) between the different procedures are negligible, but marginally favour the minimally invasive treatments relative to surgery. Disutility associated with post-operative pain, although not severe and limited to a few days duration, affects the results in the short term (two years), demonstrating the limited effects of time to failure on differential QALYs. There are differences in treatment costs however and, with little differences in QALYs, incremental net benefits are primarily driven by costs. The model results are consistent with other studies in finding that QALY differences between treatments are very small.[82;83] That of Gohel is also a modelling study comparing different treatments for varicose veins.[82] However, in other respects the results of this model are different. Gohel estimated the costs of treatments from basic units of resource

(day case, outpatient, equipment costs) and reports day case surgery to be more costly than any of the minimally invasive treatments, contrary to more recently published cost studies showing the costs of EVLA and RFA to be greater than those for surgery.[32;33] Gohel also finds surgery to be more effective than the minimally invasive treatments, on the basis of much more limited effectiveness data than used in the current analysis.

The new treatments have additional implications for training and the availability of equipment. It is possible that there are learning curve effects because the technology is continuing to develop and there are various options for some aspects of the treatment, such as timing and dosage of energy exposure, which are continuing to be investigated. Some of the earlier studies used devices or techniques that have already been superseded and it is possible that greater experience and more widespread adoption will result in improved outcomes and reduced complications. However, there may also be issues of the availability of the necessary skills and equipment, with the resource implications of providing training in the new methods.

The overall results of this research differ from the findings of other published systematic reviews and meta-analyses[84-89] in their conclusion that FS, EVLA and RFA offer potentially equally effective alternatives to surgery and, in the case of FS, a cost-effective alternative also. This difference can be explained by the inclusion of more RCT evidence in the present report (approximately three times as many relevant RCTs than any previous review, despite broader criteria in the majority of the previous reviews), the exclusion of non-RCT and non-comparative evidence, and the analysis methods used. The recently published clinical practice guidelines from both NICE[22] and the Society for Vascular Surgery and American Venous Forum[90] also recommend EVLA, RFA and FS as effective alternatives to surgery and other modalities, but the latter only cites a small number of RCTs with short-term follow-up, and one or two of the reviews cited here. Also, recent NICE guidance recommends EVLA and RFA, if suitable, as initial treatment, before using FS or surgery, although this report has found that FS is potentially the most cost-effective treatment over longer time horizons. None of the previously published reviews or analyses acknowledged the limitation presented by the use of technical recurrence evidence, rather than symptomatic technical recurrence as an outcome.

Other than the limitations of the technical recurrence data, the principal uncertainties affecting the analyses are in the cost differentials between treatments, which are likely to vary with setting, and may vary over time. There was very limited data on the costs of the different

procedures, but threshold analysis showed that the additional costs of EVLA and RFA would have to be not more than £50 and £24 more than surgery, respectively, to be considered cost-effective at a threshold of £20,000. The differences in clinical effectiveness (time to recurrence, post-operative pain) were small. The vast majority of the trials were conducted in Western Europe in populations who would typically present in the UK with varicose veins and be treated with one of the modalities assessed, so the external validity of the evidence is relatively strong for the NHS.

This assessment of the evidence suggests there is little to choose between the minimally invasive techniques in terms of technical recurrence, VCSS, pain and adverse events, and each offers a viable, clinically effective alternative to surgical stripping. Foam sclerotherapy might offer the most cost-effective alternative to surgery, within certain time parameters. Training and experience in the minimally invasive techniques might be required before relative benefits are apparent. Future trials should aim to measure and report outcomes in a standardised manner, which would permit more efficient pooling of their results, e.g. mean and Standard Deviation (SD) of all validated and commonly-used measures, such as VCSS and EQ-5D. Trial authors should also report both technical and symptomatic recurrence, to permit assessment of likely retreatment rates and costs, and utilise surgeons with adequate experience of the minimally invasive techniques, if the comparison with surgery (currently the most common procedure performed by all surgeons) is to be internally valid.

Figure 1: Model structure

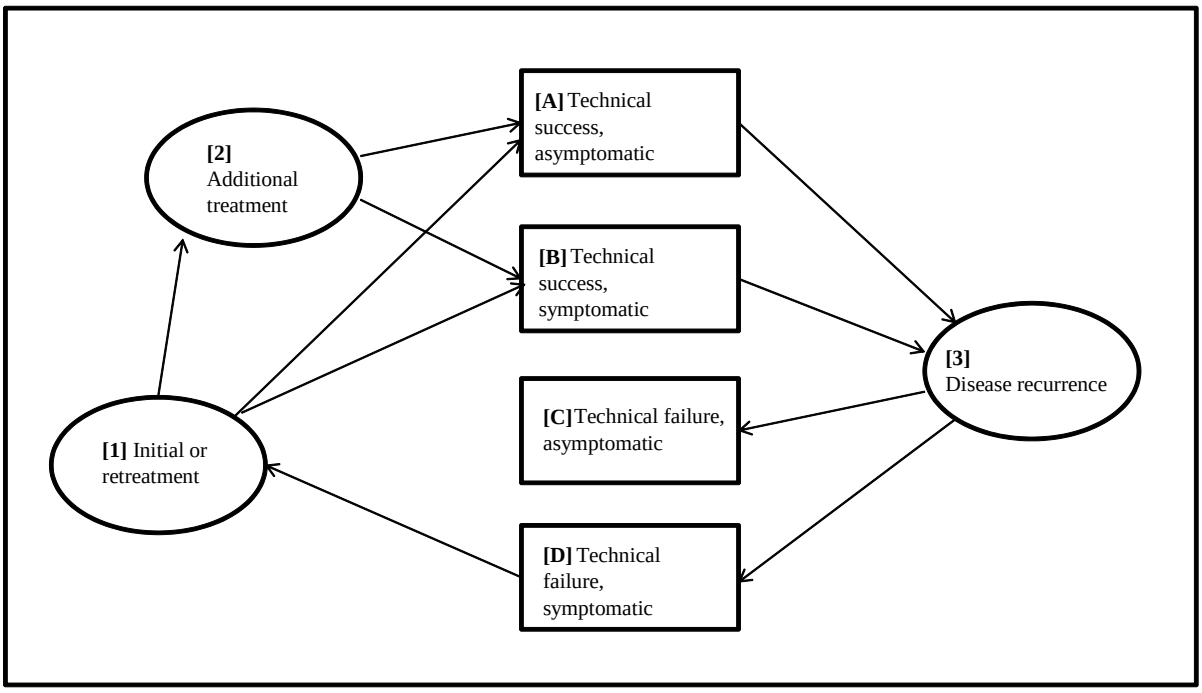


Figure 2: Initial procedure costs estimated relative to surgery costs (31;32;34)

Procedure	Cost relative to surgery	Initial procedure cost	Source
Surgery	-	£1,155	National reference costs
Foam sclerotherapy	0.55	£634	Bountouroglou 2006
RFA	2.28	£2,635	Subramonia 2010
EVLA	2.02	£2,338	See text

Figure 3: PRISMA flowchart

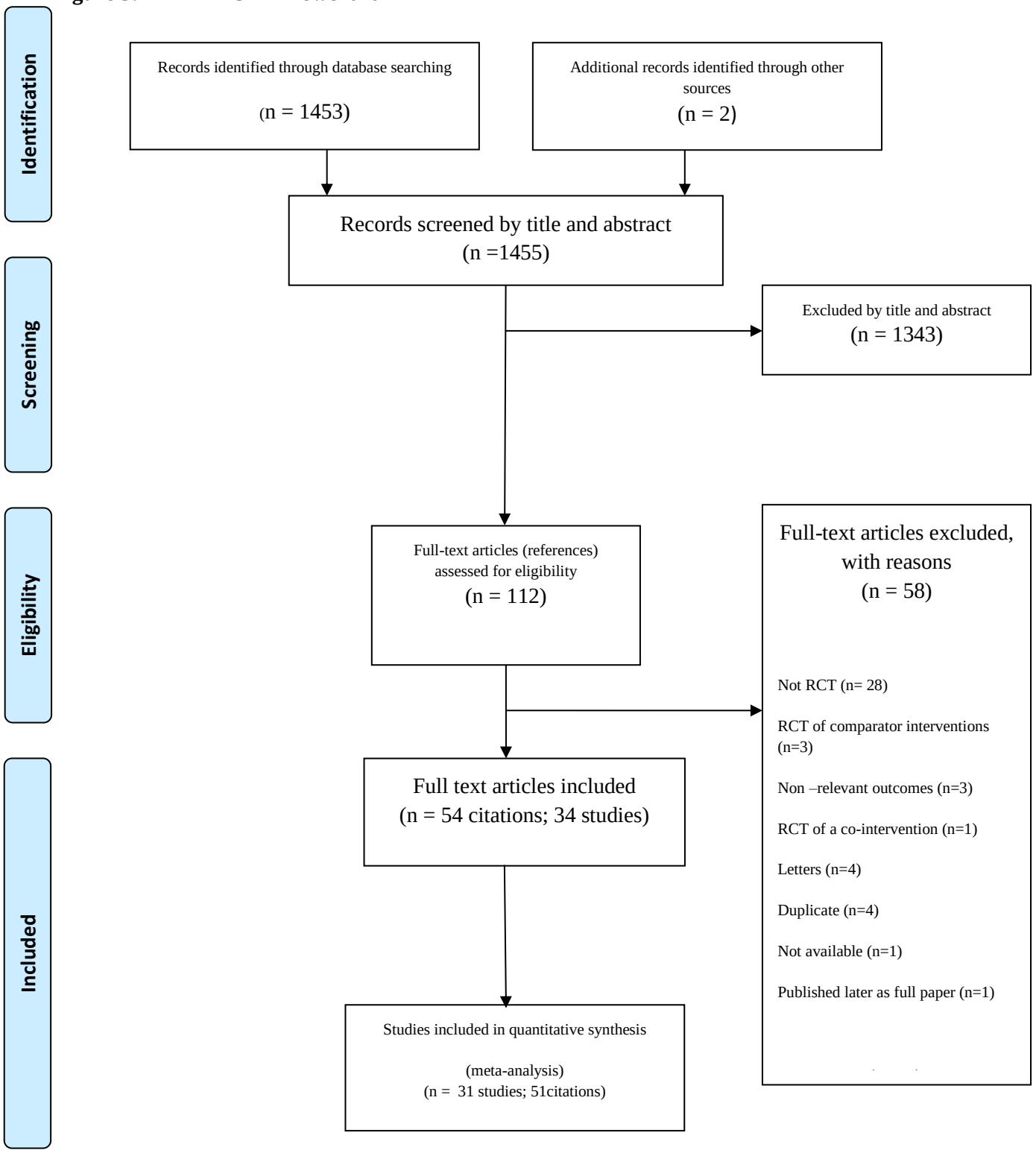


Figure 4: Technical recurrence: Posterior distribution for the hazard ratios relative to surgery at 6 months, 1 year and 2 years

	6 Months **Median** **(95% CrI)** **[Probability HR >1]**	**1 Year** **Median** **(95% CrI)** **[Probability HR >1]**	**2 years** **Median** **(95% CrI)** **[Probability HR >1]**
EVLA vs. surgery	0.70 (0.27, 1.45) [0.150]	0.77 (0.37, 1.54) [0.182]	0.84 (0.44, 1.81) [0.257]
RFA vs. surgery	0.92 (0.39, 2.11) [0.409]	0.93 (0.42, 2.22) [0.411]	0.94 (0.42, 2.51) [0.421]
FS vs. surgery	1.12 (0.53, 2.27) [0.659]	1.02 (0.49, 1.84) [0.524]	0.92 (0.43, 1.60) [0.359]

Technical recurrence: the presence of reflux, recanalisation or new varicose veins in a treated limb, diagnosed by duplex ultrasound scanning (DUS); CrI: Credible interval; HR: Hazard ratio; EVLA: Endovenous laser ablation; RFA: Radiofrequency ablation; FS: Foam sclerotherapy

Figure 5: VCSS: Posterior distribution for the mean difference compared to surgery

	Median **(95% CrI)**	**Probability of mean difference >0**
EVLA vs. surgery	-0.10 (-0.94, 0.73)	0.324
RFA vs. surgery	0.15 (-0.50, 0.95)	0.739
FS vs. surgery	-1.63 (-2.90, -0.42)	0.015

CrI: Credible interval; EVLA: Endovenous laser ablation; RFA: Radiofrequency ablation; FS: Foam sclerotherapy

Figure 6: Pain scores: Posterior distribution for the mean difference compared to surgery

	Median (95% CrI)	**Probability of mean difference >0**
EVLA vs. surgery	0.10 (-0.49, 0.64)	0.653
RFA vs. surgery	-1.26 (-1.95, -0.61)	0.001
FS vs. surgery	-0.80 (-1.93, 0.30)	0.062

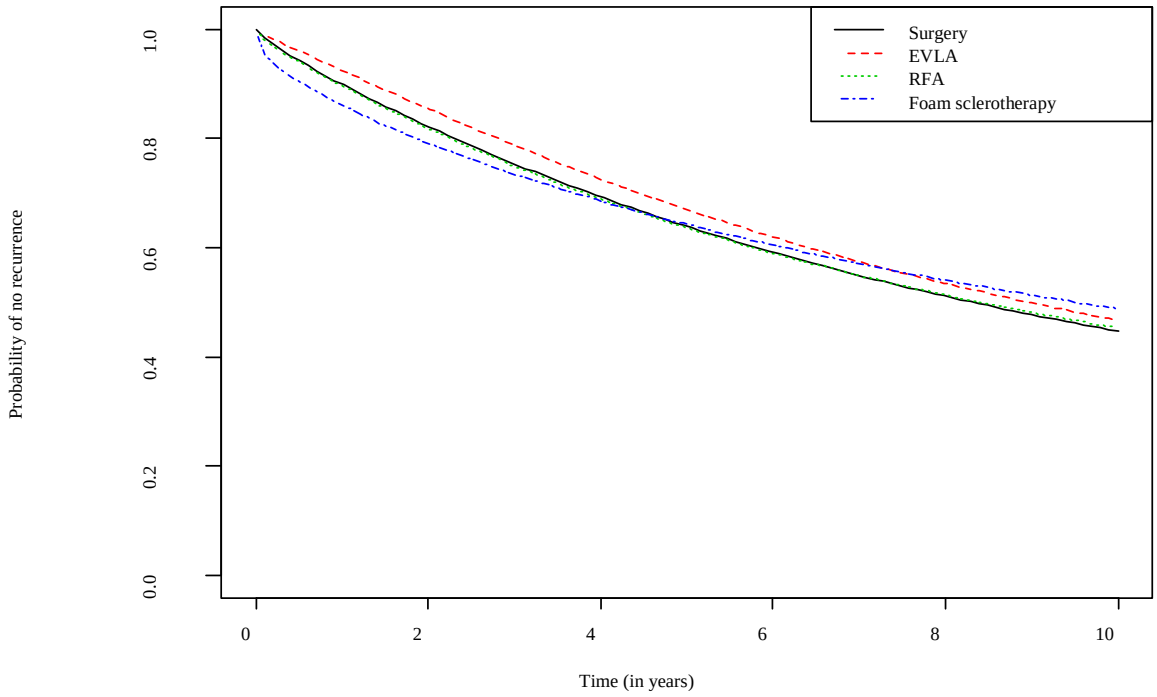
CrI: Credible interval; EVLA: Endovenous laser ablation; RFA: Radiofrequency ablation; FS: Foam sclerotherapy

Figure 7: Results of the discounted Probabilistic Sensitivity Analysis. An economic analysis of treatments for varicose veins

	Discounted		**Incremental**		**ICER**
Procedure	**Costs**	**QALYS**	**Costs**	**QALYS**	
Surgery	£1,334	8.0347	-	-	-
Foam	£804	8.0362	-£530	0.0015	NA
EVLA	£2,637	8.0372	£1,302	0.0025	£518,462
RFA	£2,952	8.0359	£1,617	0.0012	£1,352,992

ICER: Incremental cost effectiveness ratio

Figure 8: Probability of technical recurrence by intervention (mean)



Reference List

(1) Kanwar A, Hansrani M, Lees T, Stansby G. Trends in varicose vein therapy in England: radical changes in the last decade. Ann R Coll Surg Engl 2010; **92**:341-346.

(2) Lim C, Gohel M, Shepherd A, Davies A. Secondary care treatment of patients with varicose veins in National Health Service England: at least how it appeared on a National Health Service website. Phlebology 2010; **25**:184-189.

(3) Department of Health. HES Statistics 2010-2011. http://www.hscic.gov.uk/hes [Accessed 13 February 2014].

(4) Docherty JG, Morrice JJ, Bell G. Saphenous neuritis following varicose vein surgery. Br J Surg 1994; **81**: 698.

(5) Morrison C, Dalsing MC. Signs and symptoms of saphenous nerve injury after greater saphenous vein stripping: prevalence, severity, and relevance for modern practice. J Vasc Surg 2003; **38**:886-890.

(6) Wood JJ, Chant H, Laugharne M, Chant T, Mitchell DC. A prospective study of cutaneous nerve injury following long saphenous vein surgery. Eur J Vasc Endovasc Surg 2005; **30**: 654-658.

(7) Sam RC, Silverman SH, Bradbury AW. Nerve injuries and varicose vein surgery. Eur J Vasc Endovasc Surg 2004; **27**: 113-120.

(8) Rutgers PH, Kitslaar PJ. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein. Am J Surg 1994; **168**: 311-315.

(9) Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL et al. Revision of the CEAP classification for chronic venous disorders: Consensus statement. J Vasc Surg 2004; **40**:1248-1252.

(10) Kistner R, Eklof B, Masuda E. Diagnosis of chronic venous disease of the lower extremities: the "CEAP" classification. Mayo Clin Proc 1996; **71**:338-345.

(11) Labropoulus N. CEAP in clinical practice. Vasc Surg 1997; **31**:224-225.

(12) Rutherford R, Padberg F, Comerota A, Kistner R, Meissner M, Moneta G. Venous severity scoring: An adjunct to venous outcome assessment. J Vasc Surg 2000; **31**:1307-1312.

(13) Kakkos SK, Rivera MA, Matsagas MI, Lazarides MK, Robless P, Belcaro G et al. Validation of the new venous severity scoring system in varicose vein surgery. J Vasc Surg 2003; **38**:224-228.

(14) Khilnani NM, Grassi CJ, Kundu S, D'Agostino HR, Khan AA, McGraw JK et al. Multi-society Consensus Quality Improvement Guidelines for the Treatment of Lower-extremity Superficial Venous Insufficiency with Endovenous Thermal Ablation from the Society of Interventional Radiology, Cardiovascular Interventional Radiological Society of Europe,

American College of Phlebology, and Canadian Interventional Radiology Association. J Vasc Interv Radiol 2010; **21**:14-31.

(15) Fischer R, Chandler JG, Stenger D, Puhan MA, De Maeseneer MG, Schimmelpfennig L. Patient characteristics and physician-determined variables affecting saphenofemoral reflux recurrence after ligation and stripping of the great saphenous vein. J Vasc Surg 2006; **31**:81-87.

(16) Winterborn RJ, Foy C, Heather BP, Earnshaw JJ. Randomised trial of flush saphenofemoral ligation for primary great saphenous varicose veins. Eur J Vasc Endovasc Surg 2008; **36**:477-484.

(17) 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.

(18) Campbell WB, Kumar AV, Collin TW, Allington KL, Michaels JA. The outcome of varicose vein surgery at 10 years: clinical findings, symptoms and patient satisfaction. Ann R Coll Surg Engl 2003; **85**:52-57.

(19) National Institute for Clinical Excellence. Endovenous laser treatment of the long saphenous vein. London: National Institute for Clinical Excellence (NICE) 2004.

(20) National Institute for Clinical Excellence. Radiofrequency ablation of varicose veins. London: National Institute for Clinical Excellence (NICE) 2003.

(21) National Institute for Health and Clinical Excellence. Ultrasound-guided foam sclerotherapy for varicose veins. London: National Institute for Health and Clinical Excellence (NICE) 2007.

(22) National Institute for Health and Care Excellence. Varicose veins in the legs. the diagnosis and management of varicose veins. NICE Clinical Guideline 168. 2013.

(23) Carroll C, Hummel S, Leaviss J, Ren S, Stevens J.W., Everson-Hock E et al. Clinical effectiveness and cost effectiveness of minimally invasive techniques to manage varicose veins: A systematic review and economic evaluation. Health Technol Assess (Winch Eng) 2013; **17**(48).

(24) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Inter Med 2009; **151**:264-269.

(25) Spiegelhalter D, Thomas A, Best N, Lunn D. OpenBUGS User Manual,Version 3.2.1. 2011.

(26) Lunn D, Thomas A, Best N, Spiegelhalter D. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing 2000; **10**:325-337.

(27) Brooks S.P Gelman A. Alternative methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics 1998; **7**:434-445.

(28) National Institute for Clinical Excellence. Guide to the methods of technology assessment. National Institute for Health and Clinical Excellence 2008.

(29) Shepherd AC, Gohel MS, Lim CS, Davies AH. A study to compare disease-specific quality of life with clinical anatomical and hemodynamic assessments in patients with varicose veins. J Vasc Surg 2011; **53**:374-382.

(30) Merchant RF, Pichot O, Closure Study Group. Long-term outcomes of endovenous radiofrequency obliteration of saphenous reflux as a treatment for superficial venous insufficiency. J Vasc Surg 2005; **42**:502-509.

(31) Darvall KA, Sam RC, Bate GR, Silverman SH, Adam DJ, Bradbury AW. Changes in health-related quality of life after ultrasound-guided foam sclerotherapy for great and small saphenous varicose veins. J Vasc Surg 2010; **51**:913-920.

(32) Bountouroglou DG, Azzam M, Kakkos SK, Pathmarajah M, Young P, Geroulakos G. Ultrasound-guided foam sclerotherapy combined with sapheno-femoral ligation compared to surgical treatment of varicose veins: early results of a randomised controlled trial. Eur J Vasc Endovasc Surg 2006; **31**:93-100.

(33) Subramonia S, Lees T. Radiofrequency ablation vs conventional surgery for varicose veins - a comparison of treatment costs in a randomised trial. Eur J Vasc Endovasc Surg 2010; **39**:104-111.

(34) Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J et al. Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). Health Technol Assess (Winch Eng) 2006; **10**(13):1-114.

(35) National Schedule of Reference Costs 2010-11. Department of Health. https://www.gov.uk/government/publications/2010-11-reference-costs-publication [Accessed 13 February 2014]

(36) Curtis L. Unit Costs of Health and Social Care 2011. Personal Social Services Research Unit, University of Kent . 2011.

(37) Browne J, Jamieson L, Lewsey J, van der Meulen J, Copley L, Black N. Case-mix & patients' reports of outcome in Independent Sector Treatment Centres: Comparison with NHS providers. BMC Health Serv Res 2008; **8**:78.

(38) Carradice D, Mazari FA, Mekako A, Hatfield J, Allgar V, Chetter IC. Energy delivery during 810 nm endovenous laser ablation of varicose veins and post-procedural morbidity. Eur J Vasc Endovasc Surg 2010; **40**:393-398.

(39) Carradice D, Mazari FA, Samuel N, Allgar V, Hatfield J, Chetter IC. Modelling the effect of venous disease on quality of life. Br J Surg 2011; **98**:1089-1098.

(40) Durkin MT, Turton EP, Wijesinghe LD, Scott DJ, Berridge DC. Long saphenous vein stripping and quality of life--a randomised trial. Eur J Vasc Endovasc Surg 2001; **21**:545-549.

(41) Nordon IM, Hinchliffe RJ, Brar R, Moxey P, Black S, Thompson MM et al. A prospective double-blind randomized controlled trial of radiofrequency versus laser treatment of the great saphenous vein in patients with varicose veins. Ann Surg 2011; **254**:876-881.

(42) Ara R, Brazier J. Populating an economic model with health state utility values: moving towards better practice. Value in Health 2010; **13**:509-518.

(43) Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. 2011b Randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. Br J Surg 2011; **98**:501-510.

(44) Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). J Vasc Surg 2003; **38**:207-214.

(45) Rautio T, Ohinmaa A, Perala J, Ohtonen P, Heikkinen T, Wiik H et al. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: A randomized controlled trial with comparison of the costs. J Vasc Surg 2002; **35**:958-965.

(46) Gale SS, Lee JN, Walsh ME, Wojnarowski DL, Comerota AJ. A randomized, controlled trial of endovenous thermal ablation using the 810-nm wavelength laser and the ClosurePLUS radiofrequency ablation methods for superficial venous insufficiency of the great saphenous vein. J Vasc Surg 2010; **52**:645-650.

(47) Goode SD, Chowdhury A, Crockett M, Beech A, Simpson R, Richards T et al. Laser and radiofrequency ablation study (LARA study): a randomised study comparing radiofrequency ablation and endovenous laser ablation (810 nm). Eur J Vasc Endovasc Surg 2010; **40**:246-253.

(48) Wright D, Gobin J, Bradbury A, Coleridge-Smith P, Spoelstra H, Berridge D et al. Varisolve polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. Phlebology 2006; **21**:180-190.

(49) Jia X, Liu XP, Xiong J, Zhang HP, Liu M, Du X et al. [Foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard stripping: a prospective randomized controlled trial]. [Chinese]. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 2010; **48**:1731-1734.

(50) Liamis A, Prionidis I, Mathai J, Gorton L, Browne T, Panayiotopoulos YP. Long saphenous vein reverse foam sclerotherapy with saphenofemoral junction ligation compared with head and invagination stripping: a prospective randomized trial. Phlebology 2005; **20**:149.

(51) Lin SM, Zhang ZH, Yao YD, Xiao JB. [Experience of endovenous radiofrequency combined with TriVex in treatment of chronic venous insufficiency in lower extremity]. [Chinese]. Chung-Hua Wai Ko Tsa Chih [Chinese Journal of Surgery] 2009; **47**:271-274.

(52) ElKaffas KH, ElKashef O, ElBaz W. Great Saphenous Vein Radiofrequency Ablation Versus Standard Stripping in the Management of Primary Varicose Veins-A Randomized Clinical Trial. Angiology 2011; **62**:49-54.

(53) Hinchliffe RJ, Ubhi J, Beech A, Ellison J, Braithwaite BD. A prospective randomised controlled trial of VNUS closure versus surgery for the treatment of recurrent long saphenous varicose veins. Eur J Vasc Endovasc Surg 2006; **31**:212-218.

(54) De Medeiros CAF, Luccas GC. Comparison of endovenous treatment with an 810 nm laser versus conventional stripping of the great saphenous vein in patients with primary varicose veins. Dermatol Surg 2005; **31**:1685-1694.

(55) Figueiredo M, Araujo S, Barros N, Jr., Miranda F, Jr. Results of surgical treatment compared with ultrasound-guided foam sclerotherapy in patients with varicose veins: a prospective randomised study. Eur J Vasc Endovasc Surg 2009; **38**:758-763.

(56) Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011; **98**:1079-1087.

(57) Christenson JT, Gueddi S, Gemayel G, Bounameaux H. Prospective randomized trial comparing endovenous laser ablation and surgery for treatment of primary great saphenous varicose veins with a 2-year follow-up. J Vasc Surg 2010; **52**:1234-1241.

(58) Darwood RJ, Theivacumar N, Dellagrammaticas D, Mavor AI, Gough MJ. Randomized clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. Br J Surg 2008; **95**:294-301.

(59) Kalteis M, Berger I, Messie-Werndl S, Pistrich R, Schimetta W, Polz W et al. High ligation combined with stripping and endovenous laser ablation of the great saphenous vein: early results of a randomized controlled study. J Vasc Surg 2008; **47**:822-829.

(60) Lawaetz M, Rasmussen LH, Bjoern L, Blemings A, Eklf B. Randomized trial comparing RF, laser, foam sclerotherapy and stripping in varicose veins. Phlebology Conference: 11th Meeting of the European Venous Forum, EVF 2010 Antwerp Belgium 2010; **25**:307.

(61) Pronk P, Gauw SA, Mooij MC, Gaastra MT, Lawson JA, van Goethem AR et al. Randomised controlled trial comparing sapheno-femoral ligation and stripping of the great saphenous vein with endovenous laser ablation (980 nm) using local tumescent anaesthesia: one year results. Eur J Vasc Endovasc Surg 2010; **40**:649-656.

(62) Morrison N. Saphenous ablation: what are the choices, laser or RF energy. Semin Vasc Surg 2005; **18**:15-18.

(63) Shepherd AC, Gohel MS, Brown LC, Metcalfe MJ, Hamish M, Davies AH. Randomized clinical trial of VNUS ClosureFAST radiofrequency ablation versus laser for varicose veins. Br J Surg 2010; **97**:810-818.

(64) Subramonia S, Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. Br J Surg 2010; **97**:328-336.

(65) Disselhoff BC, der Kinderen DJ, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser ablation of the great Saphenous vein with and without ligation of the sapheno-femoral junction: 2-year results. Eur J Vasc Endovasc Surg 2008; **36**:713-718.

(66) Kalodiki E, Azzam M, Kakkos SK, Zambas N, Bountouroglou D, Geroulakos G. Ultrasound-guided foam sclerotherapy combined with saphenofemoral ligation versus surgical treatment of varicose veins: intermediate results of a randomized controlled trial. Phlebology 2008; **23**: 242-243.

(67) Darvall KA, Bate GR, Adam DJ, Bradbury AW. Recovery after ultrasound-guided foam sclerotherapy compared with conventional surgery for varicose veins. Br J Surgy 2009; **96**:1262-1267.

(68) Abela R, Liamis A, Prionidis I, Mathai J, Gorton L, Browne T et al. Reverse foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to

standard and invagination stripping: a prospective clinical series. Eur J Vasc Endovasc Surg 2008; **36**:485-490.

(69) Alos J, Carreno P, Lopez JA, Estadella B, Serra-Prat M, Marinel-Lo J. Efficacy and safety of sclerotherapy using polidocanol foam: a controlled clinical trial. Eur J Vasc Endovasc Surg 2006; **31**:101-107.

(70) Hamel-Desnos C, Desnos P, Wollmann JC, Ouvry P, Mako S, Allaert FA. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. Dermatol Surg 2003; **29**:1170-1175.

(71) Rabe E, Otto J, Schliephake D, Pannier F. Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. Eur J Vasc Endovasc Surg 2008; **35**:238-245.

(72) Ouvry P, Allaert FA, Desnos P, Hamel-Desnos C. Efficacy of polidocanol foam versus liquid in sclerotherapy of the great saphenous vein: a multicentre randomised controlled trial with a 2-year follow-up. Eur J Vasc Endovasc Surg 2008; **36**:366-370.

(73) Rasmussen LH, Bjoern L, Lawaetz M, Lawaetz B, Blemings A, Eklof B. Randomised clinical trial comparing endovenous laser ablation with stripping of the great saphenous vein: clinical outcome and recurrence after 2 years. Eur J Vasc Endovasc Surg 2010; **39**:630-635.

(74) Belcaro G, Cesarone MR, Di RA, Brandolini R, Coen L, Acerbi G et al. Foam-sclerotherapy, surgery, sclerotherapy, and combined treatment for varicose veins: a 10-year, prospective, randomized, controlled, trial (VEDICO trial). Angiology 2003; **54**:307-315.

(75) Carradice D, Mekako AI, Mazari FA, Samuel N, Hatfield J, Chetter IC. 2011a Clinical and technical outcomes from a randomized clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. Br J Surg 2011; **98**:1117-1123.

(76) Goode S. A Randomised Study Comparing Endovenous Laser Ablation and Radiofrequency Ablation for the Treatment of Varicose Veins. European Society for Vascular Surgery Annual Meeting; 2008 Sep 4 7; Nice, France 2008;65.

(77) Stotter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping, and cryostripping in the treatment of great saphenous vein insufficiency. Phlebology 2006; **21**:60-64.

(78) Perala J, Rautio T, Biancari F, Ohtonen P, Wiik H, Heikkinen T et al. Radiofrequency endovenous obliteration versus stripping of the long saphenous vein in the management of primary varicose veins: 3-year outcome of a randomized study. Ann Vasc Surg 2005; **19**:669-672.

(79) Disselhoff BCVM, Kinderen DJD, Kelder JC, Moll FL. Randomized clinical trial comparing endovenous laser with cryostripping for great saphenous varicose veins. Br J Surg 2008; **95**:1232-1238.

(80) Shadid N, Nelemans P, Sommer A. Duplex-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein: A randomized controlled trial. Phlebology Conference: 11th Meeting of the European Venous Forum, EVF 2010 Antwerp Belgium 2010; **25**:306-307.

(81) Rasmussen LH, Lawaetz M, Serup J, Bjoern L, Vennits B, Blemings A et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. J Vasc Surg: Venous and Lymphatic Disorders 2013; **1**:349-356.

(82) Gohel MS, Epstein DM, Davies AH. Cost-effectiveness of traditional and endovenous treatments for varicose veins. Br J Surg 2010; **97**:1815-1823.

(83) Disselhoff BC, Buskens E, Kelder JC, der Kinderen DJ, Moll FL. Randomised comparison of costs and cost-effectiveness of cryostripping and endovenous laser ablation for varicose veins: 2-year results. Eur J Vasc Endovasc Surg 2009; **37**:357-363.

(84) Jia X, Mowatt G, Burr JM, Cassar K, Cook J, Fraser C. Systematic review of foam sclerotherapy for varicose veins. Br J Surg 2007; **94**:925-936.

(85) Luebke T, Brunkwall J. Systematic review and meta-analysis of endovenous radiofrequency obliteration, endovenous laser therapy, and foam sclerotherapy for primary varicosis. J Cardiovasc Surg 2008; **49**:213-233.

(86) Luebke T, Gawenda M, Heckenkamp J, Brunkwall J. Meta-analysis of endovenous radiofrequency obliteration of the great saphenous vein in primary varicosis. J Endovasc Ther 2008; **15**:213-223.

(87) Murad MH, Coto-Yglesias F, Zumaeta-Garcia M, Elamin MB, Duggirala MK, Erwin PJ et al. A systematic review and meta-analysis of the treatments of varicose veins. J Vasc Surg 2011; **53**:49S-65S.

(88) Nesbitt C, Eifell R, Coyne P, Badri H, Bhattacharya V, Stansby G. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus conventional surgery for varicose veins. Cochrane Database Syst Rev 2011.

(89) van den Bos R, Arends L, Kockaert M, Neumann M, Nijsten T. Endovenous therapies of lower extremity varicosities: A meta-analysis. J Vasc Surg 2009; **49**:230-239.

(90) Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML et al. 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 2011; **53**:2S-48S.