Systematic review

Systematic review, network meta-analysis and exploratory cost-effectiveness model of randomized trials of minimally invasive techniques *versus* surgery for varicose veins

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Background: **A Health Technology Assessment was conducted to evaluate the relative clinical effectiveness 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 randomized clinical trials (RCTs) was undertaken 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: 31 RCTs (51 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 FS 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 were similar to those for 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 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 cost of the treatments becomes one of the deciding factors. High-quality RCT evidence is needed to verify and further inform these findings.**

Paper accepted 17 April 2014
Published online 25 June 2014 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9566

Introduction

The prevalence of varicose veins in the UK has been reported to be between 20 and 40 per cent in adults. The National Health Service (NHS) performed over 33 000 surgical procedures to treat varicose veins in 2010–2011. 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 NHS[2,3], although there are regional variations in the types of procedure performed[2]. However, ligation and stripping has been associated with a range of adverse effects such as wound infection, haematoma, leakage of lymph, pain, scarring, nerve injury, deep vein thrombosis (DVT) and prolonged postoperative 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 (Clinical Etiologic Anatomic Pathophysiologic) classification[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 using the Venous Clinical Severity Score (VCSS)[12,13]. The VCSS may be used to gauge clinical severity before and after intervention – to measure the efficacy of an intervention.

The higher the score, the worse the disease severity. The presence of venous reflux is identified principally by duplex ultrasonography (DUS). The indication of pathological reflux is the presence of reversed venous flow for more than 0·5 to 1·0 s after proximal compression, the Valsalva manoeuvre, or distal compression and release[14].

The principal outcomes associated with treatment of varicose veins are symptom relief and symptom severity, recurrence of varicosities, as well as the occurrence of new varicosities in the same leg, and retreatment. Reported recurrence rates vary widely depending on the nature of the surgical technique and the method of assessment. For conventional ligation and stripping surgery, 2-year recurrence rates of up to 33 per cent have been reported[15,16], rising to 41 per cent at 5 years and to up to 70 per cent at over 10 years[17,18]. Surgical procedures for recurrence can therefore place considerable demand on health services. Other outcomes of interest are health-related quality of life (HRQoL), patient treatment satisfaction, and the occurrence of related postoperative complications.

New minimally invasive treatments offer alternative methods of ablating incompetent veins, particularly the great saphenous vein (GSV). These treatments typically involve use of laser (endovenous laser ablation, EVLA)[19], radiofrequency probe[20] or foam sclerosant[21]. They are used increasingly widely 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)[22] recommends the use of EVLA or radiofrequency ablation (RFA); if this is considered unsuitable, foam sclerotherapy (FS) should be employed, and, if FS is deemed unsuitable, surgery should be used. 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]. The study aimed to evaluate the clinical effectiveness 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 randomized clinical 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 (the procedure was incomplete, or occlusion/obliteration was not achieved or was not sustained for more than 1 month); technical recurrence (as distinct from the initial episode – the presence of reflux, recanalization or new varicose veins in a treated leg) diagnosed by DUS; VCSS; pain; time to return to work or normal activity; and postoperative 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 (the minimally invasive techniques). The 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, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, Biological Abstracts, Science Citation Index, Social Sciences Citation Index, Conference Proceedings Citation Index – Science (CPCI-S), UK Clinical Research Network (UKCRN), Current Controlled Trials and ClinicalTrials.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 standard form and 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 checked for accuracy by a second. Discrepancies were resolved by discussion between reviewers. Blinding of patients and of 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. Randomization and analysis in the primary studies was described as being by patient or by leg when patients had unilateral treatment; when patients had bilateral treatment, randomization was by leg. Data were therefore all per leg or per patient; no data were per procedure (there were no occasions where multiple procedures were conducted on the same leg). The analysis was conducted using Markov chain Monte Carlo simulation implemented in the OpenBugs[25] and WinBUGS[26] software packages. The principal analysis compared the hazard of having technical recurrence after treatment with EVLA, RFA or FS, relative to the common comparator of surgery, using a complementary log–log link function and assuming that the underlying survivor functions followed 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 cost-effectiveness model was developed as a discrete event simulation (DES) model in SIMUL8® (SIMUL8 Corporation, Boston, Massachusetts, USA) 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 10 years, chosen as a reasonable time over which to extrapolate the time to failure data. Costs were reported in 2011–2012 British Pounds 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 per cent, as recommended by NICE[28]. Both probabilistic and deterministic sensitivity analyses were undertaken.

Model structure

The model structure is illustrated in *Fig. 1*. Ovals represent events (numbered 1–3) and oblongs health states (A–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 or 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, although 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[29] of FS no correlation was found between changes in the Aberdeen Varicose Veins Questionnaire, a patient-reported measure of outcomes and quality of life, and venous refill times. In addition, Merchant and colleagues[30] reported a high proportion of patients experiencing symptom improvement despite anatomical failure following RFA (70–80 per cent, compared with 85–94 per cent in legs with anatomical success). 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 from all-cause mortality.

Adverse events, other than postoperative 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

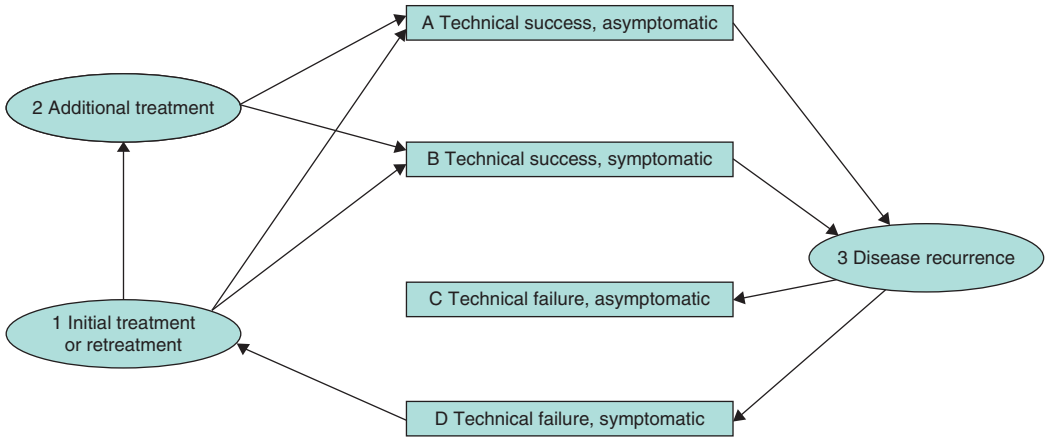

Fig. 1 Model structure

that DVT following treatment for varicose veins is rare and so any possible effects on the model results were estimated to be negligible.

Model parameters

Uncertainty about parameters representing disease recurrence data and postoperative pain were sourced from the network meta-analysis (see Results). The proportion of patients requiring treatment for initial failure (treatment failure by 1 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 per cent of late (after 1 month) retreatments were surgical procedures (stripping) and 40 per cent FS. The proportion of patients who were 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 £1420 at 2011–2012 prices[32–34]. The cost for surgery was therefore taken from National Reference costs[35], but these do not differentiate between the other treatment methods. The cost of other treatments relative to surgery was published in only a small number of studies, so this information had to be used to calculate their cost, as shown in *Table 1*. 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 (general practitioner and outpatient visits, DUS) associated with retreatment was estimated and costed using standard sources[35,36].

Table 1 Initial procedure costs estimated relative to surgery costs

Procedure	Cost relative to surgery	Initial procedure cost (£)	Source
Surgery	–	1155	Department of Health[35]
FS	0·55	634	Bountouroglou *et al.*[32]
RFA	2·28	2635	Subramonia *et al.*[33]
EVLA	2·02	2338	See text

FS, foam sclerotherapy; RFA, radiofrequency ablation; EVLA, endovenous laser ablation.

To derive an estimate of the utility associated with symptomatic varicose veins, a meta-analysis was undertaken of all studies reporting baseline (pretreatment) EQ-5D™ (EuroQol Group, Rotterdam, The Netherlands) 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 (standard error 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 1. In the model, age-specific utility is calculated by multiplying the state utility by the age-dependent utility. Loss of utility associated with postoperative pain was estimated

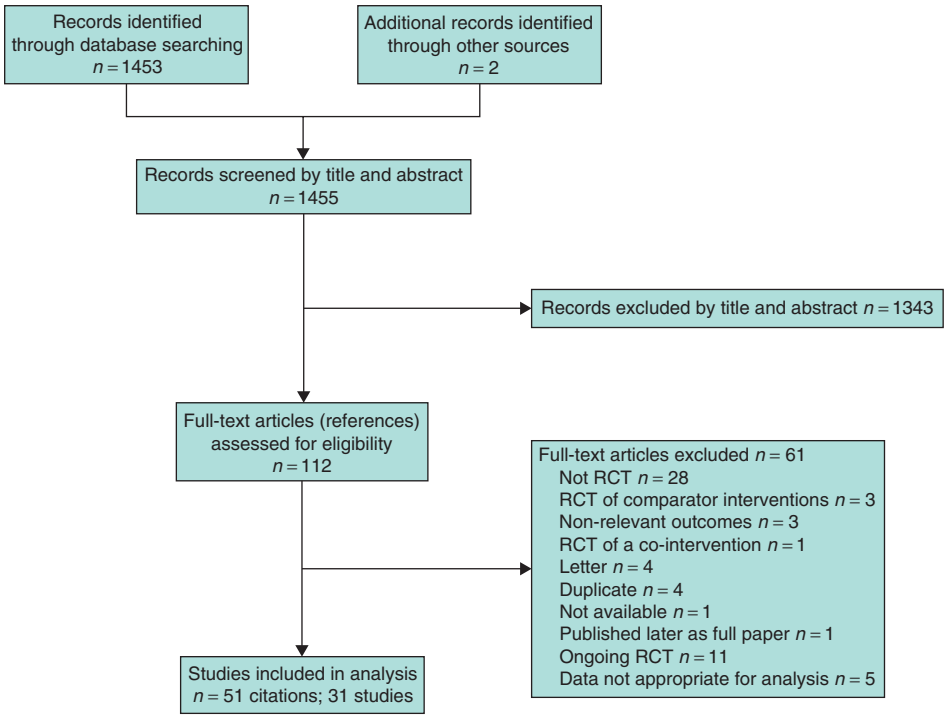

Fig. 2 PRISMA flow chart showing selection of articles for review. RCT, randomized clinical trial

from a single study[43] reporting both. The reduction in EQ-5D™ utility for each absolute 1 per cent increase in visual analogue scale (VAS) pain score was 0·0026. All parameter values are reported in *Table S1* (supporting information), except time to recurrence.

Results

Clinical effectiveness review

Included studies

The searches identified 1453 unique citations (*Fig. 2*). Eleven citations represented relevant ongoing trials and 51 citations, representing 31 different studies, provided data used in the network meta-analyses. Study characteristics for these trials are shown in *Table S2* (supporting information)[32,41,43–75]. Fourteen trials evaluated EVLA against surgery, RFA or FS; 12 trials compared RFA with surgery, EVLA, FS or other comparators; and 12 evaluated FS, comparing it principally with conventional surgery. One trial[55] had arms comparing all three minimally invasive techniques. No trial included conservative management as a comparator. The principal, common comparator was surgery.

A total of 3772 participants were randomized across all trials. The number of participants in a single trial ranged from 28[62] to 425[70]. The mean age of participants ranged from 33 years[58,62] to 54 years[59]. There was a majority of women in every trial: the proportion ranged from 52 per cent[58] to 95 per cent[47]. In all trials participants were required to have varicose veins diagnosed by DUS and categorized according to the CEAP score. The majority of participants in any trial were C2 on the CEAP score (varicose veins), except for three trials, where the majority were C3[59], C4[67] or C5[66]. The UK was the single most frequent location (12 trials); the remainder were conducted in centres across 13 other different countries.

Quality of included studies

The methodological quality assessment of each included study is summarized in *Table S3* (supporting information). The majority of the trials used in the network meta-analyses (for example those reporting technical recurrence data for EVLA *versus* surgery, or EVLA *versus* RFA, etc.) were at risk of either selection or attrition bias owing to inadequate randomization, allocation concealment or intention-to-treat analysis. Only four[49,50,54,56] 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.

Table 2 Technical recurrence: posterior distribution for hazard ratios relative to surgery at 6 months, 1 year and 2 years

	Hazard ratio		
	6 months	1 year	2 years
EVLA *versus* 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 *versus* 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 *versus* 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)

Values are median (95 per cent credible interval) (probability of hazard ratio greater than 1). Technical recurrence was indicated by the presence of reflux, recanalization or new varicose veins in a treated leg, diagnosed by duplex ultrasonography. EVLA, endovenous laser ablation; RFA, radiofrequency ablation; FS, foam sclerotherapy.

Recurrence

The principal outcome reported by trials was technical recurrence, as defined above. Data were available from 23 trials[32,41,43,45–55,58,59,61,62,66–68,70,71] at various follow-up times. The results suggested that there was mild heterogeneity between studies in the shape parameter (estimated between-study s.d. 0·17, 95 per cent credible interval (cr.i.) 0·01 to 0·45), but that there was mild to moderate heterogeneity between studies in the scale parameter (0·26, 0·02 to 0·91). EVLA exhibited the lowest rates of technical recurrence relative to surgery, although there was some evidence that this benefit decreased over time (2-year hazard ratio (HR) 0·84, 95 per cent cr.i. 0·44 to 1·81) (*Table 2*). RFA was associated with a small and relatively constant lower rate of technical recurrence over time compared with surgery (2-year HR 0·94, 0·42 to 2·51). FS was worse than surgery over the first year, although there was a small benefit after 2 years (HR 0·92, 0·43 to 1·60). In each case there was considerable uncertainty about which intervention was the most beneficial.

Venous Clinical Severity Score

Thirteen studies met the inclusion/exclusion criteria for VCSS as an outcome, although 1-year data were available from only six studies[43,45,51,54,63,68]. The between-study standard deviation (s.d.) was estimated to be 0·22 (95 per cent cr.i. 0·01 to 1·79), which is indicative of mild to moderate heterogeneity in treatment effect between studies. The VCSS for both FS and EVLA was lower than for surgery, that is, patients and clinicians reported fewer clinical symptoms for these treatments compared with surgery (*Table 3*).

Pain score

Eleven trials[41,45,46,48,50,54–56,59,62,64] reported measuring pain using a form of VAS (1–10 or 1–100) for between 3 and 14 days after intervention, and were included in the network meta-analysis. The between-study s.d. was estimated to be 0·48 (95 per cent cr.i. 0·06 to 1·12), which is indicative of mild to moderate heterogeneity in treatment effect between studies. The interventions that exhibited the lowest pain scores compared with surgery were RFA (mean difference −1·26, −1·95 to −0·61) and FS (mean difference −0·80, −1·93 to 0·30) (*Table 4*).

Table 3 Venous Clinical Severity Score: posterior distribution for mean difference compared with surgery

	Median difference in VCSS	Probability of mean difference > 0
EVLA *versus* surgery	−0·10 (−0·94, 0·73)	0·324
RFA *versus* surgery	0·15 (−0·50, 0·95)	0·739
FS *versus* surgery	−1·63 (−2·90, −0·42)	0·015

Values in parentheses are 95 per cent credible intervals. VCSS, Venous Clinical Severity Score; EVLA, endovenous laser ablation; RFA, radiofrequency ablation; FS, foam sclerotherapy.

Table 4 Pain scores: posterior distribution for mean difference compared with surgery

	Median difference in pain score	Probability of mean difference > 0
EVLA *versus* surgery	0·10 (−0·49, 0·64)	0·653
RFA *versus* surgery	−1·26 (−1·95, −0·61)	0·001
FS *versus* surgery	−0·80 (−1·93, 0·30)	0·062

Values in parentheses are 95 per cent credible intervals. EVLA, endovenous laser ablation; RFA, radiofrequency ablation; FS, foam sclerotherapy.

Adverse events

In general, serious adverse events, such as DVT or pulmonary embolism were rare. Eleven studies reported on these outcomes, but only five[51,54,55,70,71] reported that any such complication had actually occurred. The three trials reporting the highest numbers of these adverse events (Wright *et al.*[71], 78 events; Rasmussen *et al.*[55], 87 events; Shadid *et al.*[70], 125 events) also had the largest sample sizes of all studies included in the review[55,70,71], with Wright and colleagues[71] reporting a substantially higher rate than any other study. However, this disproportionate rate can be explained by the intervention. The VARISOLVE® (BTG, London, UK) technique applied in this trial[71] was new and the amount of foam used was altered part way through the

Table 5 Results of the discounted probabilistic sensitivity analysis; an economic analysis of treatments for varicose veins

	Discounted		Incremental		
Procedure	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£)
Surgery	1334	8·0347	–	–	–
FS	804	8·0362	–530	0·0015	n.a.
EVLA	2637	8·0372	1302	0·0025	518 462
RFA	2952	8·0359	1617	0·0012	1 352 992

QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; FS, foam sclerotherapy; n.a., not applicable; EVLA, endovenous laser ablation; RFA, radiofrequency ablation.

trial because of the high DVT rate: the initial amount of foam (60 ml) was reduced to 30 ml. No DVT was reported for the 95 participants who subsequently received this lower dose.

Summary of clinical 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 probabilistic sensitivity analysis, with costs and QALYs discounted at a rate of 3·5 per cent, are shown in *Table 5*. Although there is an element of retreatment, the total costs of treatment are comprised primarily 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 with surgery at 10 years, although the QALY differences between surgery, EVLA and RFA are negligible, equivalent to less than 1 day in full health for EVLA compared with surgery.

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 greater than 90 per cent for willingness-to-pay thresholds in the range £20 000–50 000. The incremental cost-effectiveness ratios (ICERs) for EVLA and RFA, in comparison to surgical stripping, show that they are not cost-effective at usually accepted levels[28].

The full results of the univariable sensitivity analysis have been reported elsewhere[23]. The results were not sensitive to uncertainty associated with most parameters, with the exception of the disutility associated with postoperative treatment, and the model time horizon. The results for FS compared with surgery were potentially sensitive to disutility associated with treatment, a parameter derived from the network meta-analysis of reported pain at approximately 10 days (*Table 4*). By 10 days after treatment, pain has already subsided, and therefore the analysis may not fully reflect differences between the treatments. In addition, the relationship between postoperative pain and utility was based on limited data[43].

The model time horizon has the potential to affect results owing to differences between the treatments in postoperative pain and recurrence rates (*Table 2* and *Fig. 3*). For EVLA and RFA, the incremental QALYs are greater and the costs lower with increasing time span, as their failure rates are lower than for surgery (HR at 1 year 0·77 for EVLA, 0·93 for RFA), so the ICERs are lower the longer the model time horizon. Even run for a lifetime, however, the ICERs do not approach £30 000. RFA results in less postoperative pain than EVLA, so RFA results in more QALYs at 2 years compared with EVLA, but by 10 years EVLA overtakes RFA owing 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 for

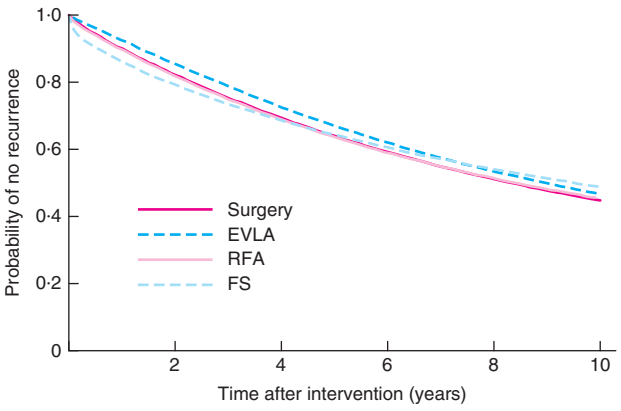

Fig. 3 Mean probability of technical recurrence by intervention. EVLA, endovenous laser ablation; RFA, radiofrequency ablation; FS, foam sclerotherapy

FS is slightly higher in the first few years compared with surgery (HR 1·02 at 1 year), potentially resulting in fewer QALYs for intermediate model time spans. In the longer term (between 10 years and life), FS has a lower failure rate than surgery and leads to a small QALY gain (*Fig. 3*).

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. The central estimate is that total FS costs are the lowest and this procedure is marginally more effective than surgical stripping (+0·0015 QALYs), with a probability of being the most cost-effective treatment above 90 per cent for willingness-to-pay thresholds in the range £20 000–50 000. This result is, however, sensitive to the model time horizon (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 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 no more than £50 and £24 respectively greater than the costs of surgery 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[76]. EVLA and RFA both cost more than surgery, and with little difference in QALYs they cannot be considered cost-effective at the usual threshold of £20 000–30 000[28]. However, there were 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 those for 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, and 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, 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 with 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 likely to present with symptoms of recurrence requiring retreatment is not certain. The rates of technical recurrence are therefore higher than those encountered in clinical practice, because non-symptomatic patients would not report, 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 owing to the relative infrequency with which such data were reported, as well as the limitations of the reporting of these data in primary studies. Based on projections from trial data, the long-term risk of a technical recurrence is less for all of 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 postoperative pain, although not severe and limited to a few days' duration, affects the results in the short term (2 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 driven primarily by costs. The model results are consistent with other studies[77,78] in finding that QALY differences between treatments are very small. Gohel and colleagues[77] also ran a modelling study comparing different treatments for varicose veins. However, in other respects the results of this model are different. Gohel and co-workers estimated the costs of treatments from basic units of resource (day case, outpatient, equipment costs) and reported day-case surgery to be more costly than any of the minimally invasive treatments, contrary to more recently published cost studies[32,33] showing the costs of EVLA and RFA to be greater than those for surgery. Gohel *et al*. also found surgery to be more effective than the

minimally invasive treatments, on the basis of much more limited effectiveness data than used in the present 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 complication rates. 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[79–84]. The present conclusion is 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 in any previous review, despite broader criteria in the majority of 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[85] also recommend EVLA, RFA and FS as effective alternatives to surgery and other modalities, but the latter cited only a small number of RCTs with short-term follow-up, and one or two of the reviews cited here. Recent NICE guidance also recommends EVLA and RFA, if suitable, as initial treatment, before using FS or surgery. The present 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 were 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 no 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, postoperative pain) were small. The great majority of the trials were conducted in western Europe, in populations that 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. FS might offer the most cost-effective alternative to surgery, within certain time parameters. Training and experience in the minimally invasive techniques may be required before relative benefits are apparent. Future trials should aim to measure and report outcomes in a standard manner, which would permit more efficient pooling of their results, for example mean(s.d.) values for all validated and commonly used measures, such as the VCSS and EQ-5D™. Trial authors should also report both technical and symptomatic recurrence, to permit assessment of likely retreatment rates and costs, and use 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.

Acknowledgements

This report was commissioned by the NIHR Health Technology assessment (HTA) programme as project number 10/29/01. This paper is an abbreviated version of the full HTA report (see reference 23).
Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Summary of model parameters (Word document)

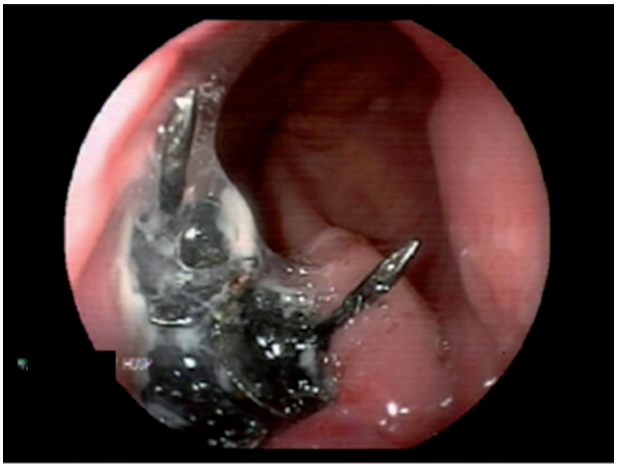
Table S2 Basic characteristics of included trials (Word document)

Table S3 Methodological quality summary: review of authors' judgements about the adequacy of each methodological quality item for each included study (Word document)

Snapshot quiz

Snapshot quiz 14/11

Question: This 75-year-old man complained of severe anal pain. He had undergone resection of his rectum for cancer 9 years previously. What does the proctoscopic image show?



The answer to the above question is found on p. 1062 of this issue of *BJS*.

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