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A Cost-effectiveness Analysis of Surgery, Endothermal Ablation, Ultrasound-guided Foam Sclerotherapy and Compression Stockings for Symptomatic Varicose Veins

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WHAT THIS PAPER ADDS

This cost-effectiveness analysis directly informed the recommendations made by NICE clinical guideline CG168, which was commissioned to reduce the uncertainty around the clinical and cost-effectiveness of these treatments. The analysis shows that interventional treatment for varicose veins is a cost-effective use of NHS resources.

Objective: The aim was to investigate the cost-effectiveness of interventional treatment for varicose veins (VV) in the UK NHS, and to inform the national clinical guideline on VV, published by the National Institute of Health and Care Excellence.

Design: An economic analysis was constructed to compare the cost-effectiveness of surgery, endothermal ablation (ETA), ultrasound-guided foam sclerotherapy (UGFS), and compression stockings (CS). The analysis was based on a Markov decision model, which was developed in consultation with members of the NICE guideline development group (GDG).

Methods: The model had a 5-year time horizon, and took the perspective of the UK National Health Service. Clinical inputs were based on a network meta-analysis (NMA), informed by a systematic review of the clinical literature. Outcomes were expressed as costs and quality-adjusted life years (QALYs).

Results: All interventional treatments were found to be cost-effective compared with CS at a cost-effectiveness threshold of £20,000 per QALY gained. ETA was found to be the most cost-effective strategy overall, with an incremental cost-effectiveness ratio of £3,161 per QALY gained compared with UGFS. Surgery and CS were dominated by ETA.

Conclusions: Interventional treatment for VV is cost-effective in the UK NHS. Specifically, based on current data, ETA is the most cost-effective treatment in people for whom it is suitable. The results of this research were used to inform recommendations within the NICE guideline on VV.

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INTRODUCTION

Visible varicose veins (VV) in the lower limbs are estimated to affect at least a third of the UK population.[1] Although in some people these veins remain asymptomatic, in others they cause symptoms such as pain, aching, or itching and can have a significant negative effect on health-related quality of life (HRQL). Symptoms may become more severe with time or complications may develop, including bleeding, thrombophlebitis, skin damage, and ulceration. One study showed that 28.6% of those who had visible VV without oedema or other complications progressed to more severe venous disease after 6.6 years.[2] A number of treatments for VV have been shown to increase HRQL[3] and are thought to slow progression of the disease. Such treatments range from compression stockings (CS), to minimally invasive (endovenous) interventional procedures (principally ultrasound-guided foam sclerotherapy, UGFS, and

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endothermal ablation, ETA), to surgery. In 2011/2012, 32,704 VV procedures were carried out in the UK NHS,[4] yet national figures suggest that the number of VV procedures undertaken in the UK is decreasing each year. In addition, the UK NHS lags significantly behind its European counterparts in terms of numbers of procedures per population; a fourfold difference can be seen between the number of procedures per million population in the UK compared with Germany.[5] Clearly there is great disparity in the way VV are treated across Europe.

Recommendations for referral were published by NICE in 2001,[6] yet the recommendations have not widely been adhered to. This has led to a "postcode lottery", and precipitated a clinical guideline on the diagnosis and management of VV, which was commissioned by the NICE.[7,8] The aim was to provide guidance on the diagnosis and management of VV in order to improve patient care and minimize regional variation across the UK. The guideline was developed through work with a multi-disciplinary Guideline Development Group (GDG), and followed the procedures set out in the guidelines manual.[9] The cost—utility analysis (CUA) outlined in this paper was developed as part of the VV guideline. Cost-effectiveness analysis is integral to the guideline process, as it allows the interventions that offer the greatest value for money to be prioritized, where clinically appropriate. Such prioritization is necessary when faced with budget constraints, as spending in one area of healthcare displaces spending elsewhere. The relevance of cost-effectiveness analysis and the implications for the treatment of VV have been discussed elsewhere.[10]

METHODS

An overview of the methods for this economic evaluation are presented here; full details can be found in Appendix L to the full guideline.[7]

An economic analysis was conducted to compare the cost-effectiveness of surgery (stripping and ligation), ETA (radiofrequency ablation, RFA, and endovenous laser ablation, EVLA, considered together), UGFS, and CS, as these were the treatments considered in the guideline. Note that the decision to consider RFA and EVLA together was made by the GDG, as the basic principle of ultrasound-guided endovenous thermal ablation is shared between the techniques and the results are very similar. For a discussion on the potential differences in costs between RFA and EVLA please refer to Appendix L of the full guideline.[7] The model considered adults with primary unilateral great saphenous vein (GSV) incompetence (chosen for being a common presentation of VV), who were potentially suitable for treatment by any of the four treatment options.

A Markov model was developed (Fig. 1). All patients were assumed to have a first treatment episode, which comprised an initial treatment and top-up treatment where necessary. Following this, the treatment episode was considered to be complete. Patients could experience clinical recurrence of VV (defined as development of symptoms of VV in a treated limb), the probability of which differed by

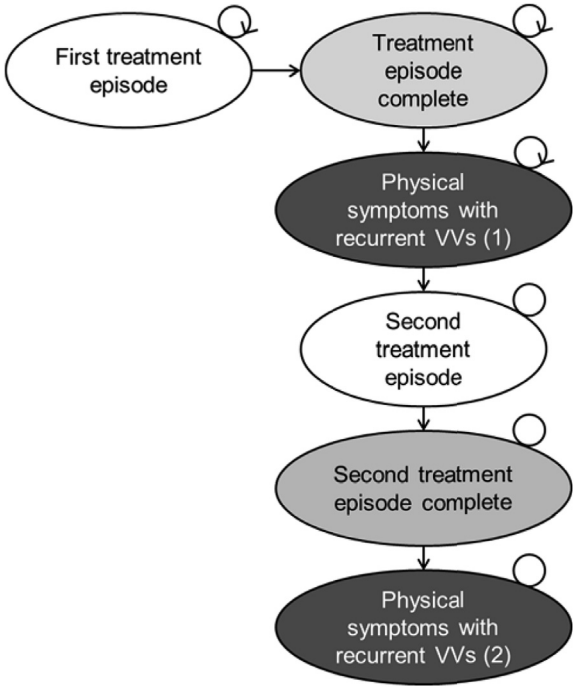

Figure 1. Model diagram. Schematic diagram of the Markov model designed to compare the cost-effectiveness of treatments for VV. The arrows denote possible transitions between states. All patients enter the model through the "First treatment episode" state. The state "Dead" was included in the model but is not shown in this diagram.

treatment option. A proportion of recurrent patients were assumed to undergo a second treatment episode (6 months after the onset of the recurrence), after which they could experience recurrence for a second time, but would not receive further treatment.

CS was modelled separately to the other three treatments, as the outcomes of completed treatment and clinical recurrence are not clinically meaningful when considering this management technique. Inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. The model cohort was assumed to be 65% female and have a starting age of 50, which was the approximate mean of all the patients from the included trials (all-cause mortality rates are age and gender specific but are unrelated to health state or treatment strategy). The model was built probabilistically to take account of the uncertainty surrounding each input parameter. Various deterministic sensitivity analyses were also undertaken to test the robustness of the model to different assumptions and data sources (deterministic sensitivity analysis involves varying the inputs of the model, in order to investigate the effect they have on the results). The model was built with a 1-month cycle length (chosen as this was deemed to be the minimum clinically meaningful time interval to detect differences between interventions), over a time horizon of 5 years in the base case. A time horizon of 5 years was chosen as clinical data were only available for a follow-up of 3 years, and the GDG did not feel

Table 1. Overview of parameters and parameter distributions used in the model.

Parameter description	Point estimate	Probability distribution	Distribution parameters	Source
Utility weights				
Primary VV	0.764	Beta	$\alpha = 37600$, $\beta = 12800$	PROMs[3]
Change in utility (from baseline) post treatment	+0.091	Lognormal	$\mu = -2.397$, $\sigma = 0.0007$	PROMs[3]
Change in utility (from baseline) due to recurrent VV	−0.093	Lognormal	$\mu = -2.206$, $\sigma = 0.0128$	Beresford et al.[13]
Conservative care (relative to surgery at 1 year)	−0.101	Normal	$\mu = 0.101$, $\sigma = 0.0198$	Michaels et al.[15]
Transition probabilities				
Probability of requiring top-up treatment (within 2 months post treatment)				
Surgery	5%	Deterministic SA only		GDG estimate
Endothermal	5%	Deterministic SA only		GDG estimate
Foam Sclerotherapy	20%	Deterministic SA only		GDG estimate
Conservative care	NA			
Probability of recurrence (per month)				
Surgery	0.0083 (SD 0.0031)	Point estimate and uncertainty from NMA		
Endothermal	0.0058 (SD 0.0134)	Point estimate and uncertainty from NMA		
Ultrasound-guided foam sclerotherapy	0.0091 (SD 0.0037)	Point estimate and uncertainty from NMA		
Conservative care	NA			
Cost (£)				
Surgery	£908	Gamma	See Appendix L to the full guideline — only NHS reference cost components modelled probabilistically	See Appendix L to the full guideline for full breakdown of costs and sources
Endothermal	£624	Gamma		
Ultrasound-guided foam sclerotherapy	£315	Gamma		
Conservative care[a]	£234	Deterministic SA only		
Additional cost associated with retreatment	£417	Gamma	See Appendix L to the full guideline — only NHS reference cost components modelled probabilistically	See Appendix L to the full guideline for full breakdown of costs and sources

GDG = guideline development group; NMA = network meta-analysis; PROMs = patient-reported outcome measures; SA = sensitivity analysis; SD = standard deviation.

[a] This is an annual cost (first year incurs an additional £15).

that basing long-term extrapolation on arbitrary assumptions in the absence of data was appropriate.

Probabilities

Clinical recurrence (network meta-analysis). A network meta-analysis[11] was conducted to calculate treatment-specific probabilities of clinical recurrence. In order to account for the different follow-up times of the various trials, an underlying Poisson process with a constant event rate was assumed for each trial arm, and a complementary log—log (cloglog) link function used to model the event rate. A key assumption employed here is a constant hazard of recurrence — this was deemed to be a reasonable simplifying assumption as the time horizon of the model is relatively short.

Surgery was chosen as the baseline comparator as it featured in all the trials. The baseline hazard was estimated on the cloglog scale through a meta-analysis of the surgery arms of the included trials. The resulting predictive distribution for the baseline hazard was combined with treatment-specific hazard ratios resulting from the network meta-analysis to calculate the probability of clinical recurrence for each treatment. The codes for both the baseline and relative effects models were adapted from that provided on the NICE Decision Support Unit (DSU) website,[12] and run in WinBUGS 1.4. The baseline and relative effects models were run for a sample of 50,000 iterations after an initial 'burn in' of 50,000 iterations. Convergence was checked through examination of trace and history plots.

Top-up treatment and re-treatment. The model assumed that all top-up treatments were UGFS; this assumption does not impact recurrence rates, it only impacted costs, which were thoroughly explored through sensitivity analyses. The purpose here was to include a cost of top-up treatment to capture the increased cost if some procedures require more top-ups than others. The choice of top-up treatment was therefore not of primary relevance.

Not all patients were expected to be retreated after experiencing clinical recurrence; the GDG estimated that 75% of patients would receive further interventional treatment, and it was assumed that the remaining 25%

would receive CS. The proportion of patients undergoing each modality of re-treatment was assumed to be independent of the modality of their initial treatment (Table 1).

Utilities

In CUA, measures of health benefit are valued in terms of quality adjusted life years (QALYs). A QALY is a measure of a person's length of life weighted by a valuation of their HRQL over that period. The weight used is called a utility value, which is a measurement of the preference for a particular health state, with a score usually ranging from 0 (death) to 1 (perfect health). Utility inputs for the model were taken from the patient-reported outcome measures (PROMs),[3] and are documented in Table 1. The baseline value was used in the model to represent the utility of a patient with primary VV, that is when a patient first receives treatment. The health gain after treatment was used to model the increase in utility associated with treatment.

The HRQL associated with recurrent VV was taken from Beresford et al.,[13] and the SF-36 data provided in the paper were mapped to EQ-5D utility scores, using an established equation developed by Ara and Brazier.[14]

As mentioned previously, CS was modelled separately to the main analysis. The difference in utility between patients undergoing surgery and CS was used to calculate the difference in QALYs over time between these two treatments. The difference in utility between these two treatments was taken from Michaels et al.[15] (Table 2) as this was the only paper found to report such data. For the probabilistic analysis the difference between utility following CS and surgery was modelled using a Normal distribution to allow positive and negative differences.

Costs and resource use

Costs were expressed in 2013 UK pounds and were considered from a UK NHS and personal social services perspective. Costs and QALYs were both discounted at 3.5% per annum, in accordance with the NICE reference case.

NHS reference costs do not distinguish between the various treatments for VV, so the GDG decided on a bottom-up costing approach. Resource use was estimated by the clinical members of the GDG, and where possible unit costs for these resources were collected from nationally available lists, such as the NHS reference costs or the PSSRU. Only NHS reference cost components were modelled probabilistically, and this was done using a Gamma distribution. A summary of the costs used in the model is presented in Table 1; the breakdown of the costs is presented in Appendix L of the full guideline. Costs were subject to extensive deterministic sensitivity analyses.

Calculating cost-effectiveness

Incremental cost-effectiveness ratios (ICERs) are commonly used in cost-effectiveness analysis. ICERs are calculated by dividing the difference in costs between two alternatives by the difference in QALYs. Then, if the resulting ICER falls below a given cost per QALY threshold, the more clinically effective treatment is considered to be cost effective. The cost per QALY threshold suggested by NICE is £20,000 per QALY gained.[16]

For a given cost-effectiveness threshold, cost-effectiveness can also be expressed in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (£20,000 in this case) and then subtracting the total costs (formula below).

$$\text{NMB} = \text{MeanQALYs} \times £20{,}000 - \text{MeanCosts}$$

The most cost-effective strategy is that with the highest NMB. Both methods of determining cost effectiveness will identify the same optimal strategy.

RESULTS

Network meta-analysis

Eight studies were identified from the clinical effectiveness review that included clinical recurrence as an outcome.[17–24] The network of included trials is shown in Fig. 2, with the number of trials included for each pair-wise comparison noted in parentheses. Full details of the included data are provided in Appendix L of the full guideline.

The final treatment-specific probability estimates can be seen in Table 1. The table indicates that ETA was associated with the lowest probability of clinical recurrence per month. These estimates were used to parameterize treatment effects in the decision model.

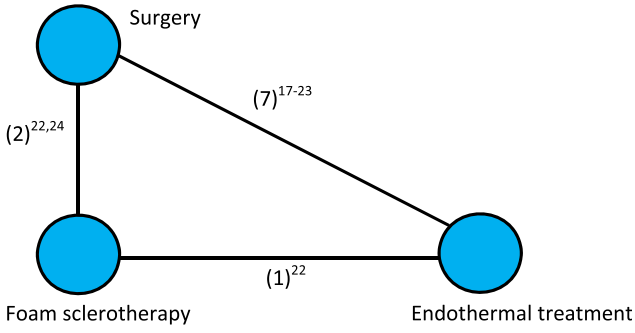

Figure 2. Network of trials compared in the network meta-analysis.

Table 2. EQ-5D data for conservative care.

Study	Relevant comparators	Utility values				
		Baseline	3 months	6 months	12 months	24 months
Michaels et al.[15] (Group 3 only: severe VV)	Surgery	0.76 (0.19)	NR	0.89 (0.13)	0.87 (0.14)	0.84 (0.21)
	Conservative care	0.77 (0.18)	NR	0.80 (0.17)	0.78 (0.18)	0.85 (0.17)

Economic model

CS and surgery dominated in the base case, as they provided fewer QALYs at increased cost compared with ETA (Table 3 and Fig. 3). ICERs are not applicable for the dominated strategies; therefore, only one ICER was calculated, comparing UGFS with ETA. Net monetary benefit (NMB) is calculated for all strategies.

ETA produced the greatest QALY gain, and was therefore the most clinically effective treatment, yet it came at an additional cost compared to UGFS, of £151 (note that this includes the downstream costs of top-up treatments and clinical recurrence, as well as the cost of the initial procedure). Using the mean costs and QALYs generated by the probabilistic sensitivity analysis, the ICER of the ETA to FS was £3,161. This is below the NICE threshold of £20,000 per QALY gained, and therefore ETA was found to be the cost-effective strategy.

In this analysis, an area of particular uncertainty is the costs. Yet, sensitivity analyses revealed that the model is robust to changes in relative costs. If the costs of surgery, UGFS, and conservative care remain as specified in the base case, ETA remains cost-effective even with increases in cost of up to £681. A wide range of further sensitivity analyses was undertaken in which key assumptions and parameters were varied. Baseline recurrence rate, utility values, time horizon, top-up rates, and modality of retreatment were among the inputs subject to such variation. An analysis was also conducted to investigate the impact of conducting ETA without concurrent phlebectomies. None of the sensitivity analyses changed the optimum result. This shows that although uncertainty surrounds model inputs and assumptions, variation within reasonable ranges does not change the results. Probabilistic analysis revealed that ETA had a probability of being cost-effective of 71% (at the threshold of £20,000 per QALY gained), followed by UGFS, which had a probability of being the most cost-effective option of 23%. The probability of each treatment being cost-effective at different threshold values is shown in Fig. 4. Full details of all sensitivity analyses and associated results are provided in Appendix L of the full guideline.

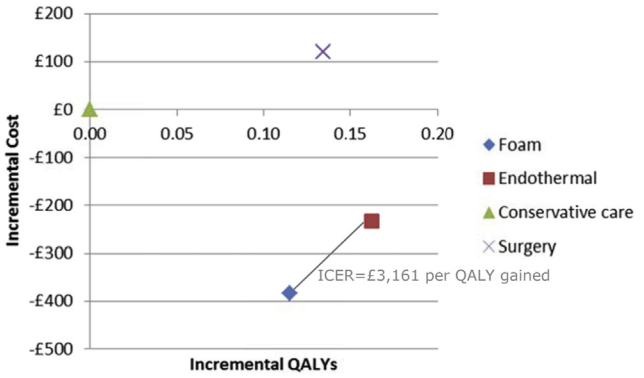

Figure 3. Cost-effectiveness plane showing incremental cost and QALYs per patient expected with each strategy (base case, probabilistic analysis).

DISCUSSION

The most important finding of this study is that all interventional treatments (surgery, ETA, and UGFS) for VV are cost-effective compared with compression therapy. The study also found that ETA is cost-effective compared with surgery and UGFS.

However, the findings of this study need to be carefully interpreted in the context of clinical practice. The model is based upon the treatment of unilateral GSV VV, which, although arguably the most common, are only one of many different presentations (bilateral, recurrent, small saphenous vein either alone or in combination with GSV). The model also assumes that the patient can be treated by all four modalities, which may rarely be the case.

In addition, the quantity and quality of data available for the NMA were limited, particularly for UGFS, for which only two trials were included. Of note, some concern was expressed by members of the GDG that the foam technique used in these trials was inadequate (1 trial used 3% polidocanol, 2 mL of solution mixed with 8 mL of air,[22] and the other used 3% polidocanol in a sclerosant to air ratio of 1:4[24]). Therefore, although the data comparing surgery with ETA is considered to be reasonably robust, there are residual concerns over the data for UGFS. Interestingly, results from one recent study[25] suggest little difference in quality of life outcomes between surgery, ETA, and UGFS over a 1-year period, despite differences in clinical outcomes. Clearly additional research is required in this area, a finding echoed by a recent HTA-funded systematic review.[26] Finally, there are as yet very limited data available on the long-term durability of ETA or UGFS, which makes predicting outcomes beyond a few years problematic. Clearly further long-term cohort and controlled studies are required.

This study reinforces the findings of Gohel et al.,[27] who found, based on a UK CUA, that RFA or EVLA performed as an outpatient procedure, or surgery performed as a day case procedure, are likely to be cost-effective treatments. The analysis presented here goes beyond that carried out by Gohel et al., by combining all available evidence in a network meta-analysis, and by including additional details such as the ongoing potential for recurrence of varicosities.

Table 3. Mean base case results (probabilistic).

Treatment	Mean per patient		Cost-effectiveness at a threshold of £20,000 per QALY gained		
	QALYs	Cost	NMB	Rank	Probability of being cost effective
Conservative care	3.55	£1 102	£69 965	4	4%
Surgery	3.69	£1 222	£72 554	3	3%
UGFS	3.67	£718	£72 681	2	23%
ETA	3.72	£869	£73 484	1	71%

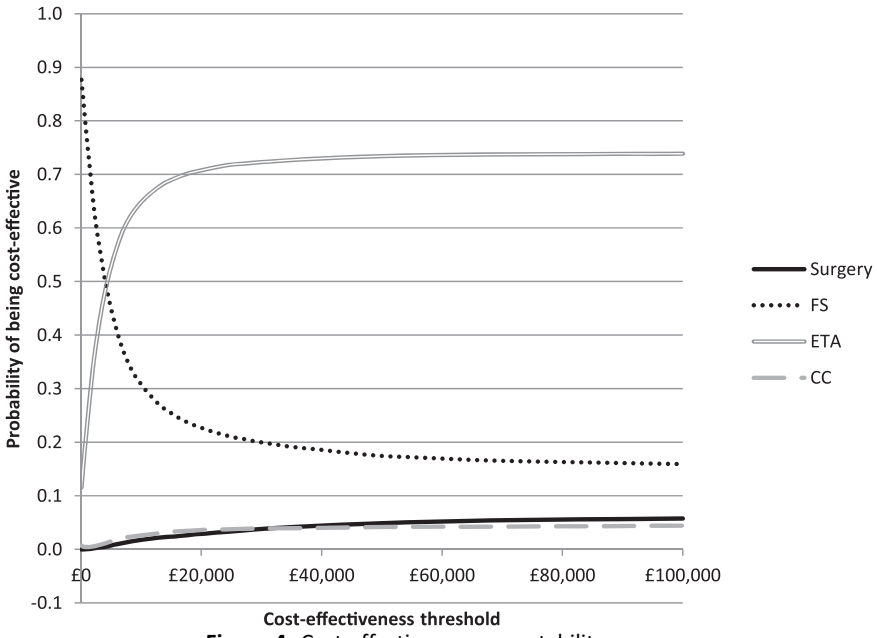

Figure 4. Cost-effectiveness acceptability curve.

A further recent UK CUA[26] found FS to be cost-effective compared with surgery, EVLA, and RFA. This study differed from the model presented here, as the analysis focused on technical (as opposed to clinical) recurrence, which included outcomes such as reflux, recanalization and incomplete obliteration of the vein all analysed together in an NMA. Using this method, little clinical difference was found between the strategies, and the model was therefore largely driven by the cost of the treatments. FS was the cheapest treatment; therefore, this was the cost-effective option in the base case. The GDG discussed this analysis at length, and raised concerns about the use of technical recurrence as a key clinical outcome (as, for example, recurrent reflux may not lead to recurrent symptoms), and about the cost figures used. Specifically, the GDG did not agree that EVLA and RFA would be more costly than surgery.

Several partial, pairwise, UK economic evaluations have also been published, where costs have been collected alongside randomized trials.[28–30] Bountouroglou et al.[29] found that foam sclerotherapy conducted under local anaesthetic costs £672.97, whereas surgery under general anaesthetic costs £1,120.64; Subramonia and Lees[30] found endothermal treatment to be more costly than surgery (£1,275.90 compared with £559.13), although the technique that was used for endothermal ablation in this trial is now considered out of date; Lattimer[28] found that foam sclerotherapy was substantially less costly than endothermal treatment (£230.24 vs. £724.72). These studies are of limited value when attempting to assess which out of all the available treatments are cost-effective, as they provide only pairwise comparisons, have relatively short follow up times, and generally don't account for recurrence or HRQL.

Throughout this analysis ETA and UGFS were assumed to take place in an outpatient setting (under local anaesthetic), and surgery as a day case procedure (under general anaesthetic). The analysis has not considered different settings of treatment, for example ETA as a day case procedure. Nevertheless, sensitivity analysis did show that the optimal strategy was fairly robust to increases in the cost of ETA and so if ETA under local anaesthetic was not considered suitable for a patient, endothermal treatment under general anaesthetic may represent a cost-effective alternative.

The results of this CUA were used to inform guideline development; therefore, ETA is the recommended strategy for treatment of truncal VV in the UK NHS, providing it is clinically and anatomically suitable for the patient. By logical extension the GDG expect that these results will hold for the treatment of the small saphenous vein,[31,32] for recurrent varicose veins, and also for bilateral treatment, again providing that ETA is deemed suitable for the patient in question. It is acknowledged within the guideline that ETA may not be suitable for all patients. If ETA is not suitable, then UGFS is considered to be the cost-effective option. If UGFS is not suitable either, surgery is the optimal strategy provided the patient is suitable and willing to be operated on.

The clinical data employed in the analysis above has been collected from around the world, yet the cost data is specific to the UK. The implication of this is that where other healthcare systems (either state or privately funded) face similar costs, and treatments can be expected to have a similar impact on quality of life, the conclusions may generalize. Indeed sensitivity analyses have shown that our conclusions are robust to substantial changes in relative costs, indicating that interventional treatment for VV may be cost-effective in various other scenarios or settings. The cost-effectiveness acceptability curve (Fig. 4) shows how the

probability of each intervention being cost-effective at different values of the cost-effectiveness threshold, which may be faced in other countries.

CONCLUSION

The model found that all interventional treatments (surgery, ETA, and UGFS) for VV are cost-effective compared with compression therapy. Based on currently available data, it is likely that endothermal treatment is the most cost-effective strategy for people in whom all treatments are suitable. When ETA is not deemed suitable for a patient, UGFS is likely to be the optimal strategy. Surgery represents the optimal choice if neither ETA nor UGFS is thought suitable.

The guideline recommends offering treatment in accordance with these findings for people with symptomatic VV. This guidance will most likely increase the number of referrals to vascular specialists, as it challenges the traditional practice of providing conservative care as a "low cost" alternative to interventional treatment. NICE estimates that much of the costs arising from the increase in referrals will be offset by a decrease in the number of expensive surgical procedures in favour of the cost-effective alternative,[33] ETA.

CONFLICT OF INTEREST

Prof. Bradbury reports grants from BTG plc, outside the submitted work; an honorarium of Euro 1000 from the European Venous Forum who have also covered travel and accommodation expenses to speak and teach on their Hands-On Workshop in Cyprus in November 2012, Stockholm in November 2013, and Tiblisi in March 2014. Also, travel and accommodation expenses to attend the Union Internationale de Phlebologie in Boston in September 2013 form STD Pharmaceuticals who make Fibrovein, which is used for foam sclerotherapy. Prof. Davies reports grants from Vascular insights, grants from Urgo Laboratoire, grants from First Kind, grants from Acergy, grants from Royal College of Surgeons, grants from NIHR, grants from BHF, outside the submitted work.

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