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The Discord Outcome Analysis (DOA) as a Reporting Standard at Three Months and Five Years in Randomised Varicose Vein Treatment Trials☆

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WHAT THIS PAPER ADDS

This paper introduces the discord outcome analysis (DOA) as a way of reporting outcomes in comparative trials on the treatment of superficial venous insufficiency. Currently, single outcome assessments are used individually resulting in very high success rates irrespective of the treatment. However, when these assessments are combined, many discrepancies are possible. For example, success in one assessment method may be met with a failure in the others. The DOA is proposed as a method of interrogating the process of reporting and the authors suggest that it becomes the adopted reporting standard to improve transparency in comparative clinical trials.

Objectives: Treatment success for chronic superficial venous insufficiency could be defined as an improvement in three domains: (i) disease specific quality of life, (ii) clinical severity, (iii) reflux. The aim was to report these at five years using a Venn diagram to profile the outcomes: a discord outcome analysis (DOA).

Methods: Patients ($n = 50$ patients/legs in each treated group) were randomised to endovenous laser ablation (EVLA) with concurrent phlebectomies vs. ultrasound guided foam sclerotherapy (UGFS). Outcomes were assessed using three domains: (i) Aberdeen varicose vein questionnaire (AVVQ), (ii) venous clinical severity score (VCSS), (iii) venous filling index (VFI) of air plethysmography. Change scores were calculated by subtracting the final score after treatment from the baseline score before treatment to quantify the improvement. This was followed by a DOA profile for each patient where a discord was defined as the percentage of patients with a numerical deterioration in one or two domains.

Results: The median [interquartile range] follow up was 68 [64–72] months. Follow up in all three domains was EVLA: 45/50, UGFS: 42/50. On ultrasound examination, GSV occlusion at some point above the knee was 93% for EVLA and 64% for UGFS ($p = .001$). There was no significant difference in improvement between the two treatment groups in the VCSS and the VFI. However, the EVLA group had a statistically significant AVVQ improvement ($p = .004$). Using a DOA, only 76% EVLA versus 60% UGFS had success in all three domains. Using improvement thresholds, this reduced to 54% and 39%, respectively. The commonest discord pattern was an improvement in the VCSS and VFI but deterioration in the AVVQ.

Conclusions: A DOA demonstrated that the definition of success is reduced if deterioration in one or two domains is taken into account. A DOA should be considered as a reporting standard for comparative analyses.

Keywords: Discord outcome analysis, Endovenous laser ablation, RCT, Ultrasound guided foam sclerotherapy, Varicose veins, Five year follow up
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INTRODUCTION

The literature is overwhelmed by randomised clinical trials (RCTs) on superficial veins which compare one treatment modality against another to determine which has the more favourable outcome.[1,2] The recipe is usually a measurement of quality of life and clinical severity using questionnaire derived scores.[3,4] This is in addition to an ultrasound assessment of saphenous occlusion rates termed a "technical success".[5] All three outcome domains have become standard reporting practice to allow meaningful comparisons between different studies.

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However, the outcomes are reported invariably using each scoring method as a separate result. If these are combined in the assessment, discrepancies may occur when one score improves while another deteriorates. This type of assessment is termed a discord outcome analysis (DOA) and has been neglected as part of the reporting recipe. Comparative studies do not focus on discord outcomes. Failure to report the discrepancies may have the effect of concealing important information and lead to the over-estimation of success.

The aim of this study was to examine the five year results from a laser versus foam RCT using change scores with a DOA. These analyses included data comparing different treatment groups as well as data from individuals where an improvement vs. deterioration is recorded as a binary result for that person.

MATERIALS AND METHODS

Study design

The details of this single centre RCT have been published.[6] It was powered on a meta-analysis which showed a five year recurrence rate (GSV recanalisation) with foam of 27% and with laser 5%.[7] For a type I error of 0.05 and a type II error of 0.2 the minimum sample size was 86. Inclusion criteria were primary symptomatic varicose veins, sapheno-femoral junction reflux, and suitability for both techniques. Exclusion criteria were sapheno-popliteal junction reflux, previous intervention, GSV diameter $>$12 mm, deep venous disease, malignancy, pregnancy, arterial disease, and coagulopathy.

In one treatment arm, 50 patients (50 legs) received endovenous laser ablation (EVLA) using the ELVeS PainLess diode 1470 nm bare tipped fibre (Biolitec, Inc. East Longmeadow, MA, USA) to a refluxing great saphenous vein (GSV). The access site was near the knee and not necessarily at the distal end point of reflux. Concurrent phlebectomies were performed under local anaesthetic. In the other arm, 50 patients (50 legs) received 1% sodium tetradecyl sulphate (STD Pharmaceuticals, Hereford, UK) into the GSV via a cannula. The foam was prepared by a two syringe agitation technique at a ratio of 1:4 sclerosant to air.

Both patient groups were given open access to supplementary foam sclerotherapy sessions at follow up. Additional treatment with UGFS was the patient's decision after discussing their post-treatment ultrasound findings. Patients were reminded of the potential side effects of foam, including pigmentation, as well as the potential benefits.

Outcome domains

The Aberdeen varicose vein questionnaire (AVVQ) was selected as the measure of disease specific quality of life.[8] It has been validated extensively and is the commonest questionnaire in use in the UK for this purpose.[9] It consists of 13 questions which are answered by the patient and is scored out of a total of 100 points to three decimal places, with a higher mark indicating a poorer quality of life.

The venous clinical severity score (VCSS) was selected as the measure of clinical severity.[10] It has been validated extensively and is recommended as a scoring system that is responsive to treatment.[11] It consists of 10 questions completed by the assessor, with each question having a score of 0—3 making a maximum of 30 severity points.

The venous filling index (VFI) of air plethysmography (APG) was selected as the measurement of haemodynamic effectiveness. It measures the rate of calf filling of the veins in mL/s, while standing, after prior leg elevation.[12] It was chosen because of its high correlation with reflux on ultrasound[13] and because reflux cannot be quantified effectively using ultrasound, especially after treatment.[14]

Ultrasound

This is a mandatory test in all endovenous treatments for superficial venous insufficiency.[15] It defines the sites of reflux pre-procedure and reports the states of occlusion, reflux, and competency after treatment.[16] It identifies reflux origins and reflux pathways down the leg. All patients were scanned with the Toshiba Xario ultrasound scanner fitted with a 6 MHz (PLT-604AT) linear array transducer (Toshiba American Medical Systems, Irvine, CA, US). Reflux was provoked using a manual calf compression and release manoeuvre with the patient standing. Reflux was defined as reverse flow lasting $>$0.5 s in saphenous trunks[17] and bidirectional flow in tributaries. Significant perforating vein reflux was defined as outward flow from deep veins feeding a downward reflux pathway.

Discord outcome analysis

The DOA is a profile of the outcome possibilities. This can be represented as a Venn diagram (Fig. 1). An improvement or deterioration was established by subtracting the post-treatment value from the pre-treatment value, to obtain a change score.[18] This was calculated for each patient on each of the three domains: AVVQ, VCSS, and VFI. A negative value defined deterioration. A positive value or no change defined improvement. These results were compared for each patient to identify a complete improvement in all three domains or the pattern of a discord outcome. As shown in Fig. 1, there are six of seven discord outcome possibilities. Deterioration in all three domains is also possible, making a total of eight outcomes.

Statistical analysis

The scores from the domains before and after treatment were entered onto spreadsheets and the data were analysed with IBM SPSS statistics package version 22 (IBM Corporation, USA). Non-parametric statistics were used with median, interquartile range (IQR), and range to define the datasets. Group performance inter-relationships were displayed using scatter plots with correlations assessed using the Spearman rho test. The Wilcoxon signed rank test was used to detect significant differences between the pre-treatment and the post-treatment values. The Mann

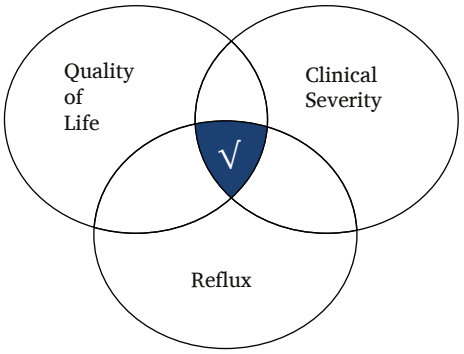

Figure 1. Three outcome domains illustrated as a Venn diagram. A global success (central tick mark) occurs with an improvement in all three domains. The six of seven other possibilities are discord outcomes.

Whitney *U* test was used to detect differences between the EVLA and UGFS groups with box plots to display the data. A $p < .05$ defined statistical significance.

Ethical approval for research

The East Midlands — Leicester Central Research Ethics Committee approved the study (REC Ref: 14/EM/1144). The clinical trials.gov identifier is: C8/4C710/87. This study is registered in the online ISRCTN registry (www.isrctn.com) and the clinical trials registration number is ISRCTN03080206.

RESULTS

General

The demographic data detailing the participant characteristics with the early and interim results have been published.[6,19] To summarise, the patients came from a multicultural and multi-ethnic background with a male to female ratio 42:58 and mild versus severe (C_{4a} and above) disease ratio 47:53 and a median refluxing GSV diameter of 7—8 mm.

The median [interquartile range] follow up was over 5 years at 68 [64—72] months. Follow up was completed across all three domains in 45/50 EVLA patients and in 42/50 UGFS patients. With ultrasound, follow up was complete in 44 legs in each group. In the EVLA group 20 additional foam sessions were performed compared with 56 additional sessions in the UGFS group, with a maximum of three additional sessions per leg.

Ultrasound

The above knee saphenous occlusion rates were in favour of EVLA ($p = .001$), as shown in Table 1. This is in agreement with most studies comparing endothermal methods with foam. However, when the definition of success changes from occlusion to a focus on reflux, the comparative results vary. In particular, there was no difference in saphenous reflux abolition above the knee ($p = .101$). Nor was there any difference in saphenous reflux abolition above plus below the knee in relation to either group ($p = .831$). Using the harsh endpoint of no reflux in the leg at all, including the tributaries (visible, palpable, and detectable only using ultrasound), then the success rate decreases to 27% in both groups. This is not too surprising because reflux is common in healthy populations,[20] and it may be argued that the extent of reflux is more important than its presence alone.

Table 1. Successful outcome variations on the GSV[a] reported with ultrasound as a percentage (%), out of 44 legs in each group

Duplex outcome at five years	EVLA[b]	UGFS[c]	*p* value[d]
AK[e] occlusion at some point	93	64	.001
AK occlusion without reflux	80	52	.013
AK and BK[f] occlusion without reflux	5	18	.089
AK without reflux	80	61	.101
AK and BK without reflux	50	46	.831
No reflux at all including tributaries	27	27	1.000

[a] Great saphenous vein.
[b] Endovenous laser ablation.
[c] Ultrasound guided foam sclerotherapy.
[d] Fisher's exact test.
[e] Above the knee.
[f] Below the knee.

The pattern of residual or recurrent reflux at five years is shown in Table 2. There are striking similarities in both groups. The commonest site of reflux was from below knee tributaries followed by the below knee GSV and then the above knee tributaries. The relevance of observing reflux alone is debateable because the question of how much reflux is clinically significant has not been answered. For this reason, ultrasound assessments were excluded from the DOA.

Correlations

The change scores (improvements) are displayed as two dimensional plots that compare the three outcomes with

Table 2. Ultrasound detected anatomical sites of venous reflux in the 32/44 EVLA and 32/44 UGFS legs which had reflux after five years

Site of reflux	EVLA[a]	UGFS[b]
GSV[c] above knee	11	15
AASV[d]	5	4
Thigh perforating vein	2	1
Above knee tributary	14	16
GSV below knee	18	18
Calf perforating vein	1	1
Below knee tributary	22	22
Small saphenous vein	4	5
Common femoral vein	1	0
Popliteal vein	0	2

Several legs had more than one site of reflux.
[a] Endovenous laser ablation.
[b] Ultrasound guided foam sclerotherapy.
[c] Great saphenous vein.
[d] Anterior accessory saphenous vein.

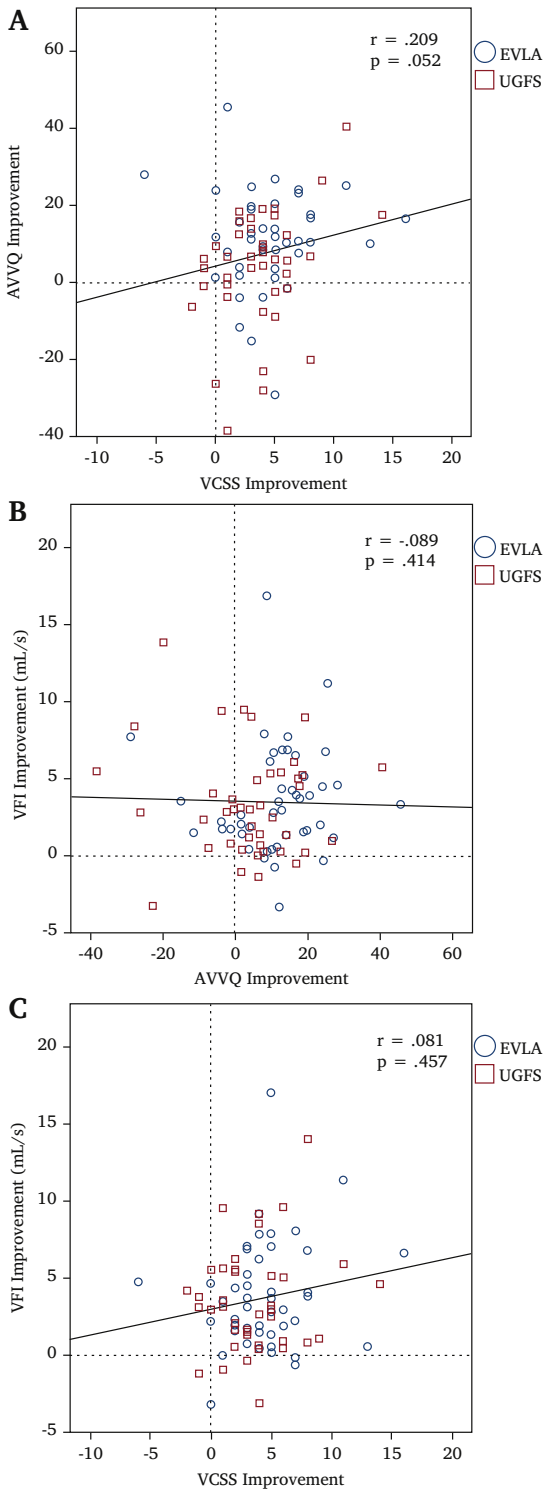

Figure 2. Scatter plots illustrating the inter-relationships between the three outcome domains at five years. The points below the horizontal dashed line or to the left of the vertical dashed line represent deterioration. Correlations (Spearman rho, r) and their statistical significance (p) are on the top right of each chart. AVVQ = Aberdeen varicose vein questionnaire; VFI = venous filling index; EVLA = endovenous laser ablation; UGFS = ultrasound guided foam sclerotherapy; VCSS = venous clinical severity score.

each other as three separate charts (Fig. 2). These display the individual data points. The poor correlations between outcomes provide fertile ground for discord outcomes. It is noticeable that in all three charts there are many points outside of the improvement quadrant, improvement defined as within the upper right quadrant of the charts A, B, and C. Seen this way, the number and extent of the discord outcomes can be appreciated within the upper left and lower right quadrants.

There were no significant correlations observed between the extents of improvements in one domain versus the improvements in another. However, the closest match was an insignificant and poor correlation between improvements in the AVVQ versus the VCSS (Fig. 2A). This is not unexpected because each domain evaluates different aspects of superficial venous insufficiency (SVI) and experienced phlebologists recognise these discords in individual patients during their everyday practice.

Treatment comparisons

In common with nearly all SVI treatment studies, improvement (post-score minus pre-score) occurred significantly in each of the three domains, irrespective of treatment group. The significance was $p < .0005$ for each situation except for the AVVQ in the UGFS group ($p = .026$, Wilcoxon, not shown). However, when improvements were compared between groups using the Mann Whitney *U* test (Fig. 3) there was no difference in significance in the VCSS or in the VFI (Fig. 3B and C, respectively). Only the AVVQ demonstrated a significant difference, statistically, in favour of EVLA at $p = .004$ (Fig. 3A). This may be related to the additional post-treatment effects in the UGFS group which received more follow up foam sessions.

Discord outcomes

None of the patients had deterioration in all three domains. The global success rate and the discord outcome possibilities are reported in Table 3. Interestingly, there were 24% discord outcomes in the EVLA group and 41% in the UGFS group, but this was not statistically significant ($p = .110$, chi-square test). The commonest discord pattern was the same in both groups, with improvement in the VCSS and VFI but deterioration in the AVVQ.

Comparisons with three month outcome data

At three months post-intervention versus pre-treatment, there was a significant improvement within all three domains in both groups at $p < .0005$ (Wilcoxon).[6] At three months, there were no significant differences in the change scores (pre-treatment minus post-treatment) between the two groups (Fig. 4). Table 3 compares the pattern of discord outcome results at three months and five years. At three months there were, in total, 15% discord outcomes in the EVLA group and 19% in the UGFS group. In common with the five year DOA, this was not statistically significant

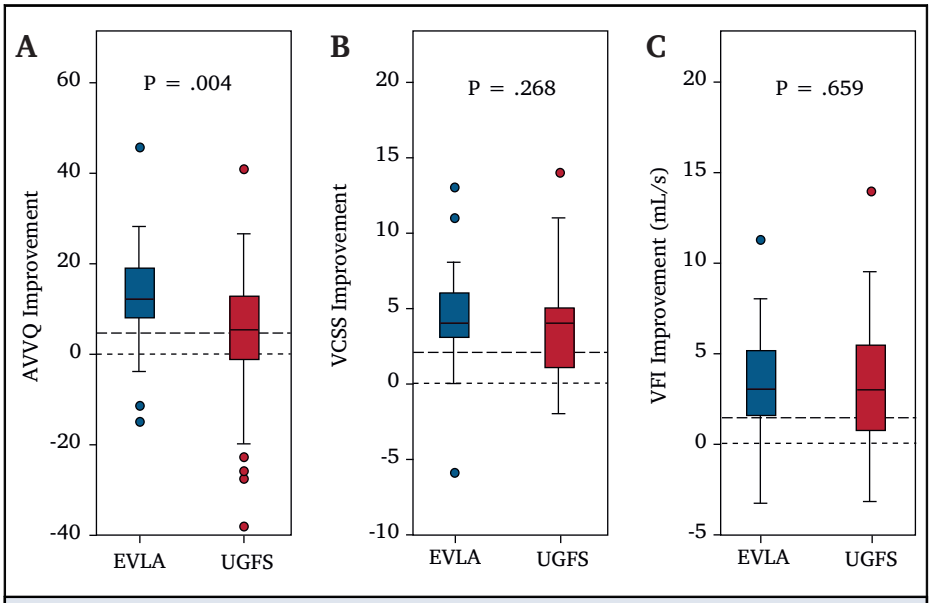

Figure 3. Box plots comparing endovenous laser ablation (EVLA) and ultrasound guided foam sclerotherapy (UGFS) in the three outcome domains. Improvement is pre-treatment score minus post-treatment score at five years. Refer to Tables 3 and 4, in which these results have been placed into the DOA profile. Statistical significance (p) is given at the top of the respective charts (Mann Whitney U test). Dashed line; numerical improvement threshold. Long dashes; clinical improvement threshold. VCSS = venous clinical severity score; VFI = venous filling index; AVVQ = Aberdeen varicose vein questionnaire; DOA = discord outcome analysis.

($p = .583$, chi-square test). Interestingly, the percentage of discord outcomes did not differ significantly between three months and five years in the EVLA group ($p = .248$), but there was a statistical increase in the UGFS group between three months and five years ($p = .027$).

DISCUSSION

This study reports the results of an RCT comparing EVLA and UGFS at a median follow up of 68 months. In contrast to most RCTs comparing interventions for SVI, there were more skin changes (lipodermatosclerosis, eczema, and pigmentation) less likely to fully resolve, larger saphenous diameters, and a greater proportion of patients with advanced disease. For this reason, many patients required treatment with UGFS during follow up in addition to the index intervention. This was required more in the UGFS group with the consequence of narrowing the discrepancies between EVLA and UGFS. As the invasiveness of subsequent UGFS is low, one might argue that it may be less effective initially, but longer term effectiveness may be enhanced with low impact repeat sclerotherapy. Taking all additional treatments with UGFS into consideration, EVLA was more effective at occluding the above knee GSV ($p = .001$). This

Table 3. The discord outcome analysis (DOA) used to compare EVLA versus UGFS treatment at three months and five years where success (√) in one domain is defined as a *numerical* improvement or no change

Numerical improvement			% patients (legs) three months		% patients (legs) five years	
AVVQ[a]	VCSS[b]	VFI[c]	EVLA[d]	UGFS[e]	EVLA	UGFS
√[f]	√	√	85 (40)	81 (38)	76 (34)	60 (25)
X[g]	√	√	9 (4)	9 (4)	13 (6)	24 (10)
√	√	X	4 (2)	6 (3)	9 (4)	5 (2)
√	X	√	(0)	(0)	2 (1)	2 (1)
X	X	√	2 (1)	(0)	0 (0)	5 (2)
√	X	X	(0)	(0)	0 (0)	2 (1)
X	√	X	(0)	4 (2)	0 (0)	2 (1)
			100 (47)	100 (47)	100 (45)	100 (42)

[a] Aberdeen varicose vein questionnaire.
[b] Venous clinical severity score.
[c] Venous filling index.
[d] Endovenous laser ablation.
[e] Ultrasound guided foam sclerotherapy.
[f] Improvement or no change before versus after treatment.
[g] Deterioration following treatment.

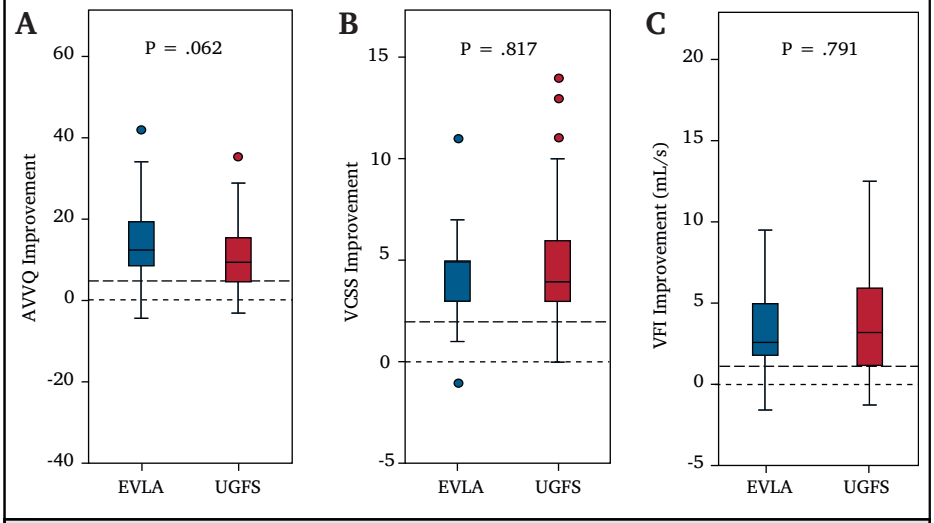

Figure 4. Box plots comparing endovenous laser ablation (EVLA) and ultrasound guided foam sclerotherapy (UGFS) in the three outcome domains. Improvement is pre-treatment score minus post-treatment score at three months. Refer to Tables 3 and 4, in which these results have been placed into the DOA profile. Statistical significance (p) is given at the top of the respective charts (Mann Whitney U test). Dashed line; numerical improvement threshold. Long dashes; clinical improvement threshold. AVVQ = Aberdeen varicose vein questionnaire; VCSS = venous clinical severity score; VFI = venous filling index.

was significant also in the absence of concurrent above knee GSV reflux ($p = .013$).

Discord outcomes are a clinical reality. This is related to the aims of the treatment, the nature of the disease of SVI, and the structure of the questionnaires as discussed below.

The main aims of treatment for SVI are to ablate the varicose veins, to alleviate leg pain or heaviness that may be attributed to venous disease, and to improve the venous drainage of a leg that is insufficient. These overlap. However, post-treatment assessments do not relate directly to the aims of the treatment. Instead, measurements are made of disease specific quality of life, clinical severity, and ultrasound occlusion rates. This provides fertile ground for discord outcomes.

The nature of SVI is that many patients do not have much pain, which is why they may present later with skin changes. This has been attributed to a lack of neural feedback when the leg undergoes gravitational stress. Venous pain is protective. This venous neuropathy has been described.[21] Furthermore, leg pain is multidisciplinary and may not relate to venous disease. The extent and distribution of varicose veins does not appear to be associated with disease severity, and it has been proposed that varicose veins may be protective by acting as a cushion that offsets direct pressure transmission down a refluxing saphenous trunk.[22] As pain and varicose veins are the more responsive parts of questionnaires following treatment, their discord with clinical severity is likely to cause assessment discrepancies.[23] A DOA will highlight these so the process of assessing SVI patients after treatment can be interrogated.

The structures of the questionnaires are such that they all summarise the disease from the phlebologist's perspective. Although the AVVQ is described as a patient reported outcome measure (PROM),[9] in reality, the scores are given a value to three decimal places by the doctor. For example, a venous ulcer (question 9) is given a high score of 9.118. This ulcer may or may not be significant to the patient irrespective of its size or duration. Another example is that purple discolouration (question 7), irrespective of its concern to the patient, is given a score of 2.000, whereas pain or ache (question 2) for more than 10/14 days is given a score of 1.812. Furthermore, only 1.875 marks of quality of life impairment are given with severe ankle swelling (question 4) where putting on shoes becomes difficult.

The other main issue with the AVVQ is that it reports disease and treatment effects in the contralateral, non-assessed leg. This may cause interference in interpretation if the AVVQ is not adjusted to account for contralateral changes, which are common after five years.[24,25] Also, current mental states such as depression or anxiety have a significant impact in AVVQ reporting.[26] Similar negative effects may be caused by questionnaire fatigue[27] and cultural differences and language problems.[28]

There are many causes for a discord outcome. Improvements in the AVVQ with deterioration in the VCSS may be caused by the successful treatment of the other leg, or just because the patient has been compliant with medical compression stockings. Conversely, improvements in the VCSS with deterioration in the AVVQ may be through an incorrect diagnosis of leg pain or because of pigmentation side effects or nerve injury. Other factors include the appropriateness of selecting patients for treatment, the quality of the data recorded, observer variations, cultural factors, and treatment differences.

A discord outcome was defined in this manuscript as a numerical deterioration in one or two of three domains. This definition could be revised into a clinical improvement

Table 4. The discord outcome analysis (DOA) used to compare EVLA and UGFS treatment at three months and five years where success (√) in one domain is defined as a *significant* improvement

Significant improvement			% patients (legs) three months		% patients (legs) five years	
AVVQ[a]	VCSS[b]	VFI[c]	EVLA[d]	UGFS[e]	EVLA	UGFS
√[f]	√	√	72 (34)	68 (31)	54 (24)	39 (16)
X[g]	√	√	7 (3)	10 (5)	20 (9)	14 (6)
√	√	X	15 (7)	12 (6)	13 (6)	14 (6)
√	X	√	2 (1)	4 (2)	7 (3)	7 (3)
X	X	√	4 (2)	(0)	2 (1)	12 (5)
√	X	X	0 (0)	(0)	4 (2)	2 (1)
X	√	X	0 (0)	6 (3)	0 (0)	10 (4)
X	X	X	0 (0)	0 (0)	0 (0)	2 (1)
			100 (47)	100 (47)	100 (45)	100 (42)

[a] Aberdeen varicose vein questionnaire.
[b] Venous clinical severity score.
[c] Venous filling index.
[d] Endovenous laser ablation.
[e] Ultrasound guided foam sclerotherapy.
[f] Significant improvement before versus after treatment.
[g] No significant change following treatment.

in only one or two domains which take into account minimally important difference (MID) values. These aim to exclude minor improvements unlikely to have a clinical effect. For example, the MID for the AVVQ is 2.4 and only improvements recorded at or above this cut off value should be used as a success.[29] As there are no MID values for the VCSS or VFI, values just a little better than the repeatability or reproducibility tolerances could be taken instead. This could be $\geq$2 points for the VCSS[30] and $\geq$1.0 points for the VFI.[31] The effect of revising the definition can be achieved by elevating the threshold in Figs. 3 and 4 using the long dashed lines. This reduces the all domain success values, irrespective of treatment, as shown on the DOA profile (Table 4 versus Table 3).

Outcomes in the treatment of SVI could be recorded in terms of improvement and deterioration across several domains. A DOA profile helps make this goal possible. It is also a way of improving existing outcome assessments by interrogating the reasons underpinning the discrepancies between the evaluation methods. The DOA is presented here as a way forward for this to take place and for consideration in the next revision of the ESVS clinical practice guidlines.[32]

CONCLUSIONS

At five years this work has shown that there is no significant difference between EVLA and UGFS in the abolition of saphenous reflux above the knee, or in the abolition of saphenous reflux above and below the knee. However, if saphenous occlusion at some point in the thigh is taken as a successful outcome then the results are significantly in favour of EVLA. No differences were detected between the groups regarding improvements in clinical severity or haemodynamic impairment. However, quality of life improvement measured with the AVVQ was statistically in favour of EVLA.

This work has demonstrated also that there were 24% discord outcomes in the EVLA group and 41% in the UGFS group. This is when improvement in one domain is met with deterioration in another. Examination as to why this has occurred may reduce the impact of success, underlining individual venous outcome assessments. We recommend that a DOA should be considered in all comparative clinical studies on treating superficial venous insufficiency.

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CONFLICTS OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.09.013.

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