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REVIEW

Commonly Used Endovenous Laser Ablation (EVLA) Parameters Do Not Influence Efficacy: Results of a Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

This study shows that all previously studied parameters of endovenous laser ablation (EVLA; wavelengths, administered energy, and definitions of outcome) have no influence on the EVLA treatment success rate. The overall success rate of EVLA is proven to be high (92%), confirming that EVLA is a highly effective treatment for incompetent great saphenous veins (GSVs), with increasing follow up. In clinical practice, this means that it is likely there will be a good treatment effect after EVLA, regardless of which (clinically studied) parameters are used.

Objectives: The objective of this systematic review and meta-analysis was to summarise available randomised controlled trials (RCTs) of EVLA efficacy, and to define the differences in success rate of variations in wavelength, administered energy, outcome definition, and follow up period.

Methods: A literature search was conducted in Embase, Medline (Ovid-SP), Cochrane Central Database, and Web of Science from inception to November 2017. RCTs with follow up of more than three months were included. The studied outcome was the proportion of patients with EVLA treatment success, defined as absence of reflux or occlusion of the great saphenous vein (GSV). Pooled proportions of anatomical success were compared. Subgroup and meta-regression analysis included wavelengths (short [810, 940, and 980 nm], long [1470, 1500, and 1920 nm]), amount of energy ($\leq$50 J/cm, $>$ 50 J/cm), follow up ($\leq$1 year, $>$ 1 year), outcome definition (occlusion, no reflux), and quality of the studies (low risk of bias, unclear/high risk of bias).

Results: Twenty-eight RCTs, with a total of 2829 GSVs were included. The overall success rate of EVLA was 92% (95% CI 90–94%, $I^2 = 68\%$). In subgroup analysis, no statistically significant differences were found for long or short wavelengths (95% [95% CI 91–97%] vs. 92% [95% CI 89–94%], $p = .15$), high or low administered energy (93% [95% CI 89–95%] vs. 92% [95% CI 90–94%], $p = .99$), long or short follow up (89% [95% CI 84–93%] vs. 93% [95% CI 91–95%], $p = .13$) and outcome definition (occlusion group 94% [95% CI 91–96%] vs. absence of reflux group 91% [95% CI 87–94%], $p = .26$). Studies with low risk of bias reported a significantly higher success rate than high or unclear risk of bias (93% [95% CI 90–95%] vs. 89% [95% CI 83–93%], $p = .04$).

Conclusions: The overall success rate of EVLA is high (92%), even with increasing follow up. Commonly used parameters of EVLA (wavelength, administered energy, and outcome definition) have no influence on the treatment success rate.

Keywords: Varicose veins, Endovascular procedures, Laser therapy, Treatment outcome

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INTRODUCTION

Several treatment options are available for patients with great saphenous vein (GSV) incompetence. In accordance with current guidelines,[1,2] endovenous laser ablation (EVLA) and other endovenous thermal ablation (EVTA) techniques have replaced high ligation and stripping as the first treatment choice for incompetent saphenous veins in many countries, as they have proven to be highly effective.[3–5]

In contrast to radiofrequency ablation (RFA), EVLA is not a standardised procedure, and can be used in many different settings. Over time, evidence of long-term follow up from well designed randomised controlled trials has become available and there has been increased variation in EVLA devices and settings used. The working mechanism of

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EVLA is not exactly known, but is mainly based on heat transfer from the EVLA fibre tip to surrounding tissue. There are some known mechanisms by which the hot fibre tip may transfer heat to the vein wall: direct contact, heat conduction, and generation of steam bubbles.[6] Although the attention in research and daily practice seems to be shifting from efficacy to patient reported outcomes, the differences in success rate for alterations in for instance wavelength, administered energy and follow up period have never been properly explored in a systematic review and pooled analyses. In the current maze of available options, the optimal effective EVLA devices or (power) settings remain under question, in terms of short and long-term efficacy. The objective of the present meta-analysis was to systematically review and summarise the available randomised controlled trials of EVLA efficacy and to define the differences in success rate of variation in wavelength, administered energy, outcome definition, and follow up.

MATERIALS AND METHODS

This review was conducted and reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA).[7]

Literature search

The search was conducted in Embase, Medline (Ovid-SP), Cochrane Central Database, and Web of Science from inception up to November 2017. The search string is provided as Supplementary material to this article. A cross reference check was performed to identify additional relevant studies.

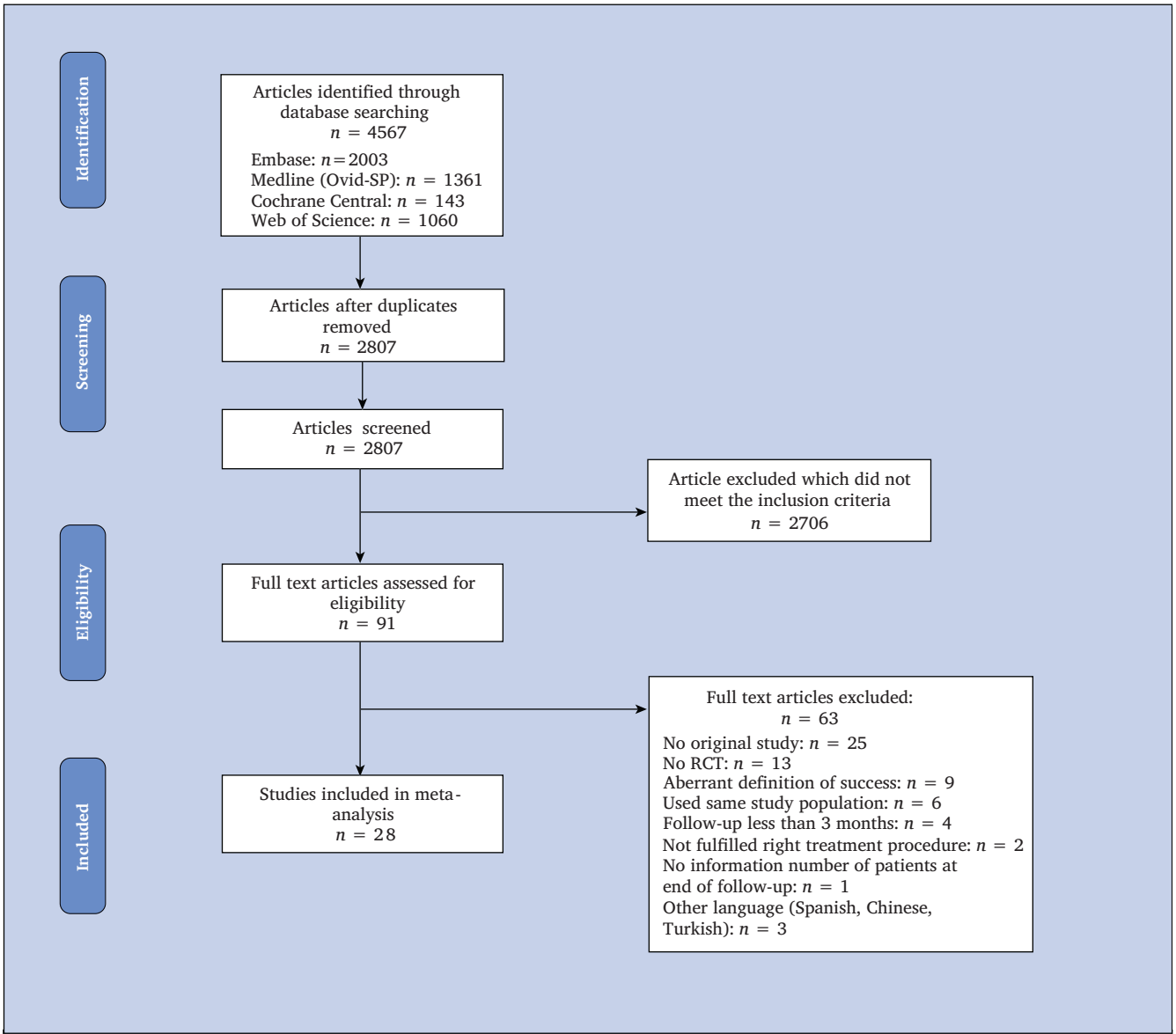

Figure 1. Flow chart of search strategy and study selection for randomised controled trials of efficacy of endovenous laser ablation. RCT = Randomised controlled trial.

Table 1. Bias assessment of randomised controlled trials of efficacy of endovenous laser ablation

Study	Year	Random assignment	Foresee assignment	Group similarity	Blinding patients	Blinding doctors	Blind assessors	Missings	Reporting bias	Other bias	Overall assessment
Sydnor[39]	2017	−	−	−	−	+	+	−	−	−	−
Venermo[20]	2016	−	−	−	+	+	?	−	−	−	−
Gauw[32]	2016	−	−	−	+	+	+	−	−	−	−
Malskat[12]	2016	−	−	−	+	+	+	−	−	−	−
Hirakowa	2015	−	−	−	+	+	+	−	−	−	−
Mendes	2015	−	−	−	+	+	+	−	−	−	−
Rass	2016	−	−	−	+	+	+	−	−	−	−
vd Velden[5]	2015	−	−	−	+	+	+	−	−	−	−
Brittenden[15]	2014	−	−	−	+	+	+	+	−	−	+
van den Bos[38]	2014	−	−	−	+	+	+	−	−	−	−
Rasmussen[16]	2013	−	−	−	+	+	+	+	−	−	+
Rasmussen[19]	2013	−	−	−	+	+	+	−	−	−	−
Samuel[37]	2013	−	−	−	+	−	+	−	−	−	−
Vuylsteke[12]	2012	−	−	−	+	+	+	−	−	−	−
Carradice[26]	2011	−	−	−	+	+	+	−	−	−	−
Disselhoff[30]	2011	−	−	−	+	+	+	+	−	−	+
Nordon[34]	2011	−	−	−	−	+	−	−	−	−	−
Christensen[27]	2010	−	−	−	+	+	+	−	−	−	−
Doganci[21]	2010	−	−	−	+	+	+	−	−	−	−
Gale[31]	2010	−	+	−	+	+	+	−	−	−	+
Goode[14]	2010	−	−	−	+	+	+	−	−	−	−
Pronk[35]	2010	−	?	−	+	+	+	−	−	−	?
Vuylsteke[23]	2010	−	+	−	+	+	+	−	−	−	+
Carradice[25]	2009	−	−	−	+	+	+	−	−	−	−
Darwood[28]	2008	?	+	−	+	+	+	−	−	−	+
Theivacumar[18]	2008	−	?	−	+	+	+	−	−	−	?
Kabnick[33]	2006	−	−	−	−	−	+	−	−	−	−
Desmyttere[29]	2005	−	−	−	+	+	+	+	−	−	+

+ = high risk of bias; − = low risk of bias; ? = unclear risk of bias.

Inclusion criteria

In this meta-analysis, only randomised controlled trials (RCTs) of treatment of primary incompetent human GSVs by EVLA were included. The studied outcome was the proportion of patients with EVLA treatment success, defined as absence of reflux or occlusion of the treated GSV. Only trials that used duplex ultrasound (DUS) examination as the outcome measure for EVLA efficacy were eligible. In comparative EVLA studies, all study arms of interest were included separately. Follow up of at least 12 weeks was required for inclusion. Only English articles were included.

Exclusion criteria

Studies that performed high ligation in combination with EVLA were excluded, as this approach may have influenced the outcome measures. Trials of EVLA treatment of perforating veins along the GSV were not included. If identical patient populations were described in different publications, the trial with the longest follow up was included. The definitions of treatment success by DUS examination varied considerably; studies that only reported "clinical recurrence," "inguinal recurrence at the saphenofemoral junction," "inguinal reflux into the great saphenous vein," or "patient satisfaction" were excluded. Also, studies without information (in the manuscript or provided by correspondence) about the number of patients examined with DUS at the end of follow up were excluded.

Data extraction

All titles and abstracts, followed by all retrieved full text articles were independently screened for relevance by two researchers (W.M. and L.E.). Disagreements were discussed and resolved. Of all included RCTs, the number of patients and treated GSVs, the EVLA wavelength(s) used, the energy administered, the duration of follow up, the US outcome definition, the number of treated GSVs available at end of follow up, and the success rate at end of follow up were extracted. Quality assessment of the studies was also performed by two independent investigators (W.M. and L.E.), according to Cochrane Collaboration's tool for assessing risk of bias in randomised trials.[8]

Statistical analysis

The primary outcome was the proportion of successful treatment (occlusion or no reflux) at the end of follow up. Data were pooled with a random effects model using the "metaprop" function from the "meta" package from R version 3.3.2 (www.r-project.org). The random effects model was chosen over a fixed effect model to allow the proportion of successful treatment to vary by study and patient level characteristics.

The I^2 was calculated and represents the amount of total variance explained by genuine differences between the studies (heterogeneity) rather than by chance because of sampling error (homogeneity). Meta-regression was

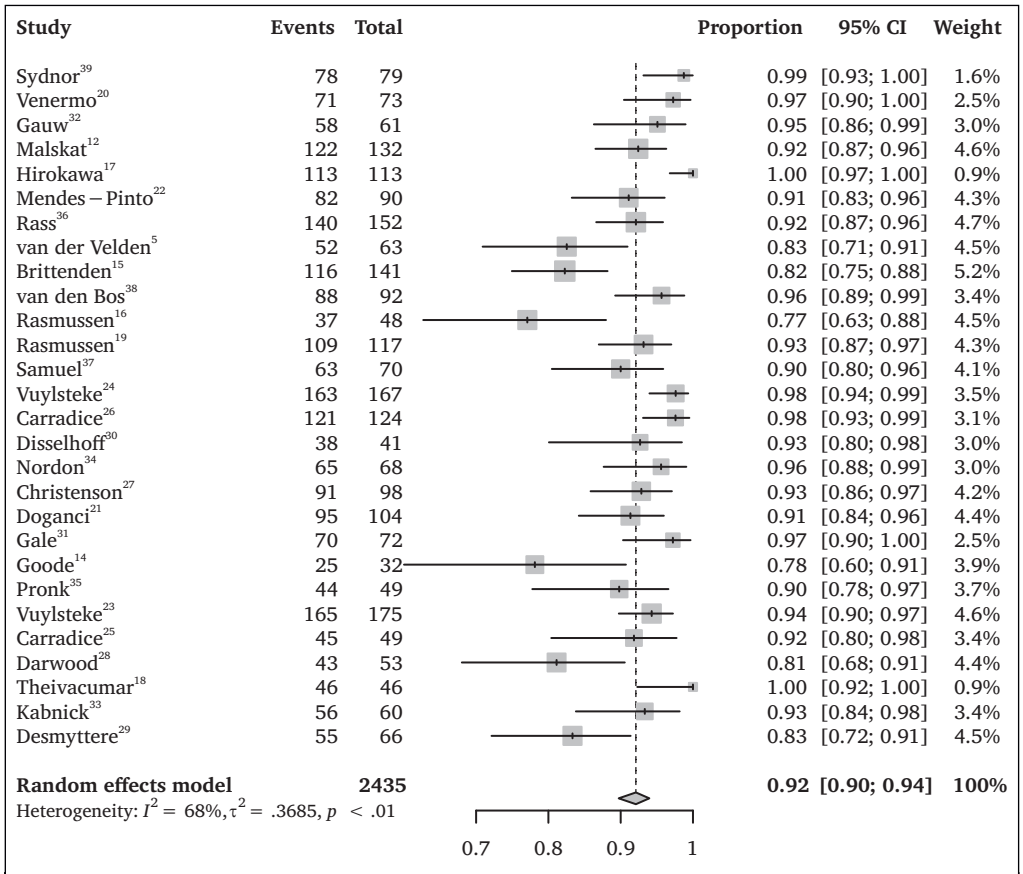

Figure 2. Overall endovenous laser ablation treatment success in randomised controlled trials. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies (92%).

Table 2. Meta-regression analysis of randomised controlled trials of efficacy of endovenous laser ablation

Study characteristic	Number of studies	Reference numbers	Pooled proportion of anatomical success [95% CI]	I^2 %	*p* value; univariable meta-regression[a]	*p* value; multivariable meta-regression[b]
Wavelength					.15	.66
High	6	11, 17, 21–24	0.95 [0.91; 0.97]	42.3		
Low	23	5, 11, 14, 16–18, 21, 23, 25-38	0.92 [0.89; 0.94]	63.6		
Energy					.99	.76
≤50 J/cm	5	11, 22, 27, 33, 36	0.92 [0.90; 0.94]	0		
>50 J/cm	20	5, 14–18, 20, 21, 24–26, 28, 30–32, 34, 35, 37, 39	0.93 [0.89; 0.95]	73.8		
Follow up					.13	.27
≤1 year	20	11, 14, 15, 17, 18, 20–26, 28, 31, 33–35, 37–39	0.93 [0.91; 0.95]	69.4		
>1 year	8	5, 16, 19, 27, 29, 30, 32, 36	0.89 [0.84; 0.93]	63.0		
Outcome					.25	.37
Occlusion	18	5, 14, 17, 18, 20–27, 29, 32–34, 39	0.94 [0.91; 0.96]	66.7		
No reflux	10	11, 16, 19, 28, 30, 31, 35–38	0.91 [0.87; 0.94]	59.9		
Risk of bias					.04	.43
Low	19	5, 11, 14, 17, 19–22, 24–27, 32–34, 36–39	0.93 [0.91; 0.95]	55.3		
High or unclear	9	15, 16, 18, 23, 28–31, 35	0.89 [0.83; 0.93]	70.2		

CI = confidence interval; I^2 = I-squared (heterogeneity).
[a] Only studies with non-missing variables were included in the analysis.
[b] Also studies with unknown variables were included in the analysis.

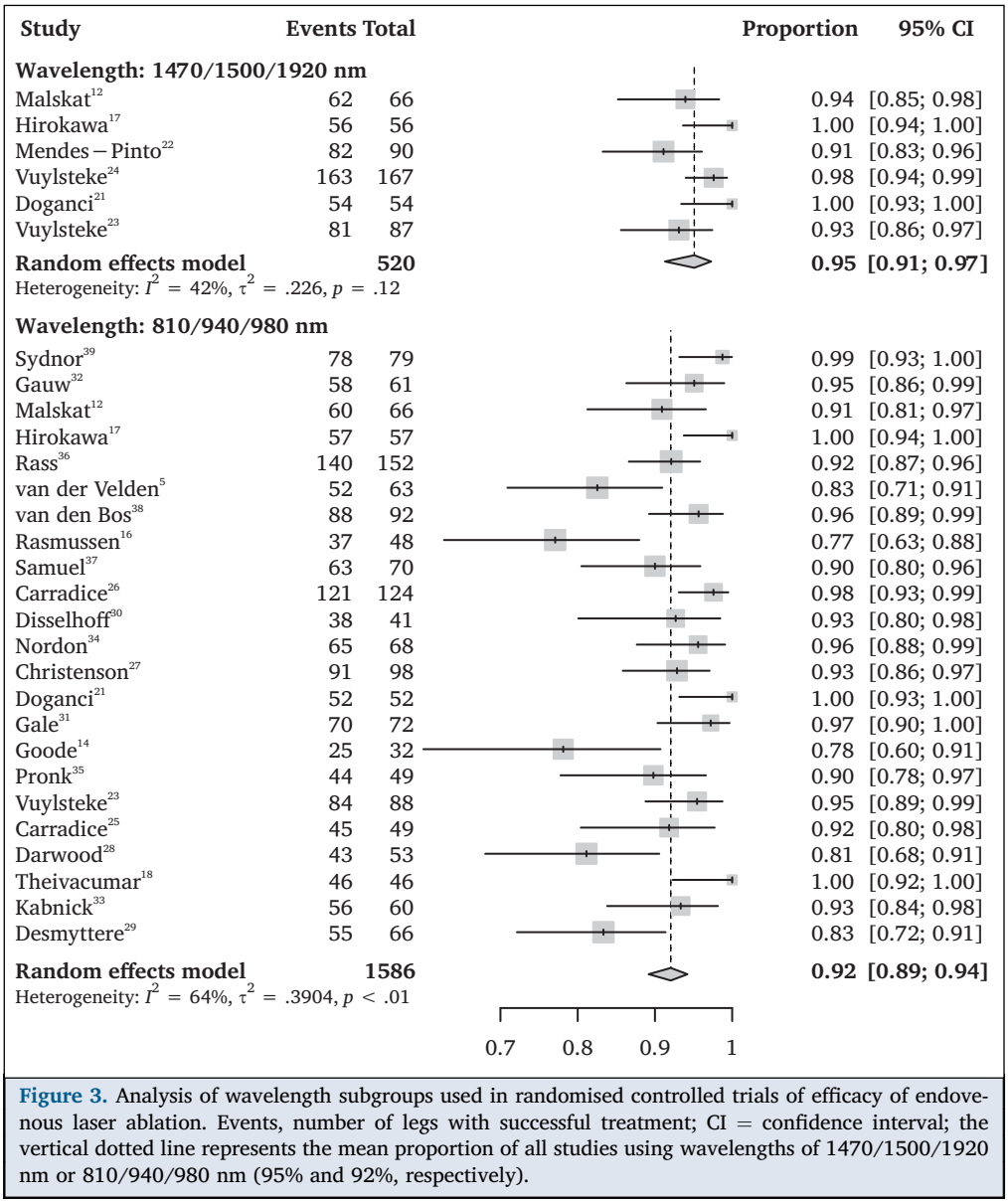

Figure 3. Analysis of wavelength subgroups used in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies using wavelengths of 1470/1500/1920 nm or 810/940/980 nm (95% and 92%, respectively).

performed to identify the possible source of heterogeneity and the model included quality of the study (low or unclear/high risk of bias),[8] duration of follow up (≤1 year, > 1 year), wavelength (Hb target [810, 940, and 980 nm], water target [1470, 1500, and 1920 nm]), energy (≤50 J/cm, > 50 J/cm [9]) and definition of successful outcome (occlusion or absence of reflux). The hypothesis was that differences in quality of the study, follow up, wavelength, energy, and outcome definition may lead to different proportions of success; it was expected that low study quality, longer follow up,[10] lower amount of energy[9,11] used, and defining occlusion as outcome (instead of absence of reflux) would result in a lower success rate, differences between wavelengths was not expected.[12] Subgroup analysis was performed to test these hypotheses and included wavelengths (short [810, 940, and 980 nm], long [1470, 1500, and 1920 nm]) amount of energy (≤50 J/cm, > 50 J/cm), duration of follow up (≤1 year, > 1 year), definition of outcome (occlusion, no reflux), and quality of the studies (low risk of bias, unclear/high risk of bias). To compare the pooled proportions of the success rates between the subgroups, univariable and multivariable meta-regression was used in which a two sided p value < 0.05 indicated statistical significance. Studies with missing values of subgroup variables were excluded from the univariable meta-regression. The multivariable meta-regression included all studies, using a "missing" category for these variables.

Sensitivity analyses included subgroup analyses with different cut off values for energy (≤40 J/cm, > 40 J/cm) and follow up (≤1 year, 1–3 years, ≥ 3 years), to examine whether lower energy is still effective, and to differentiate between short, intermediate, and long follow up period.

To detect possible publication bias, a funnel plot was constructed. For low and high proportional outcomes, traditional funnel plots (log odds of successful treatment vs.

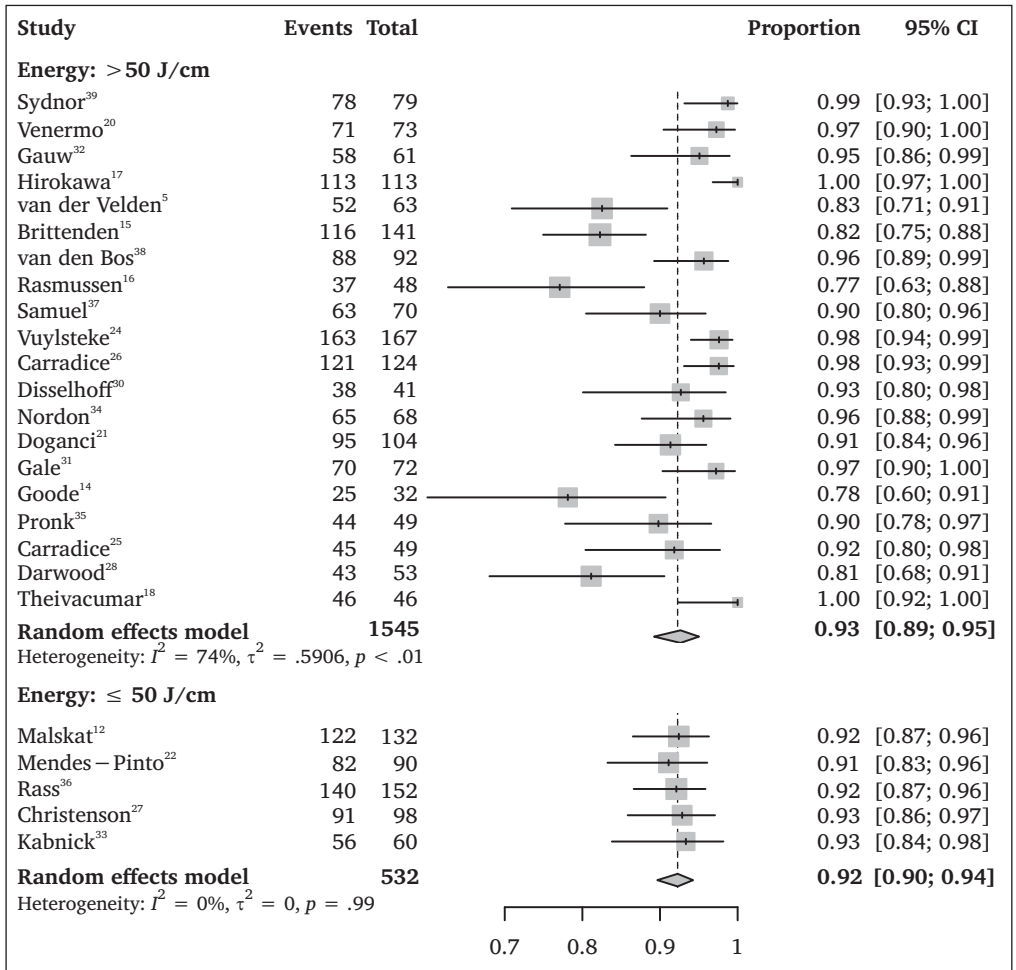

Figure 4. Analysis of energy subgroups used in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies using energy > 50 J/cm or ≤ 50 J/cm (93% and 92%, respectively).

1/SE) can result in funnel plot asymmetry without publication bias.[13] Therefore, an alternative funnel plot (sample size vs. log odds) was constructed and visually inspected. Currently there are no suitable statistical tests for funnel plot asymmetry for proportion meta-analysis.[13]

RESULTS

Study selection and characteristics

The search yielded a total of 4567 articles (Fig. 1). After deduplication, 2807 articles remained. Of these, 91 eligible studies were identified by screening title and abstract. After reading the full article texts, 28 studies met the eligibility criteria.

The general characteristics of the selected studies are presented in Supplementary Table. A total of 2829 GSVs were included in the 28 studies. The study size sample varied from 39[14] to 212[15] GSVs.

Quality of the studies/bias assessment

The risk of bias in the 28 articles was assessed as low, unclear, or high (Table 1). In most included RCTs, study treatments were technically too different, which made blinding of physicians, patients, or assessors impossible. Therefore, studies in which no blinding was applied could still be categorised as low risk of bias in the present meta-analysis. The main reasons for assessing a study as high risk of bias were reported missing outcome of more than 30% of the study population and/or unclear randomisation procedure.

Success rate

The pooled anatomical success rates are shown in Fig. 2. The overall success rate of EVLA with random effects model analysis was 92% (95% CI 90—94%, I^2 = 68%). Success rates varied from 77%[16] to 100%.[17,18]

Meta-regression and subgroup analysis

The results of uni- and multivariable meta-regression analysis are summarised in Table 2. The outcomes of the univariable meta-regression analysis are described below. There were no statistically significant differences in success rates in the multivariable model.

Wavelength. Three studies were excluded from this subgroup analysis as they used multiple wavelengths in one study arm.[15,19,20] EVLA devices with long wavelengths (1470, 1500, and 1920 nm) were used in one group in six studies,[12,17,21–24] and with short wavelengths (810, 940, and 980 nm) in (at least) one group in 23 studies[5,12,14,16–18,21,23,25–38] (Fig. 3). The success rates of long and short EVLA wavelengths were not significantly different (95% [95% CI 91–97%] vs. 92% [95% CI 89–94%], $p = .15$).

Administered amount of energy. In two studies, the administered amount of energy during treatment was unknown.[19,29] In 20 studies, > 50 J/cm was administered during EVLA,[5,14–18,20,21,24–26,28,30–32,34,35,37,39] in comparison to five studies with administered energy of ≤50 J/cm[12,22,27,33,36] (Fig. 4). There were no significant differences in success rates between these two groups (93% [95% CI 89–95%] vs. 92% [95% CI 90–94%], $p = .99$).

Follow up. The mean follow up of all studies was 20.7 months (SD 20.8). The maximum follow up was 62 months. Eight studies had a follow up of more than one year,[5,16,19,27,29,30,32,36] and 20 studies had follow up of up to one year[12,14,15,17,18,20–26,28,31,33–35,37–39] (Fig. 5). Follow up of >1 year did not correlate with a statistically significant lower success rate than ≤1 year (89% [95% CI 84–93%] vs. 93% [95% CI 91–95%], $p = .13$, respectively).

Definition of outcome. One study[15] was excluded from this subgroup analysis, as different definitions of anatomical success were used (both absence of reflux and occlusion used in the same study). In 18 studies occlusion was the stated outcome for anatomical success,[5,14,17,18,20–27,29,32–34,39] and absence of reflux in 10 studies[12,16,19,28,30,31,35–38] (Fig. 6). There was no statistically significant difference between these two outcome definitions (94% [95% CI 91–96%] in the occlusion group vs. 91% [95% CI 87–94%] in the absence of reflux group, $p = .26$).

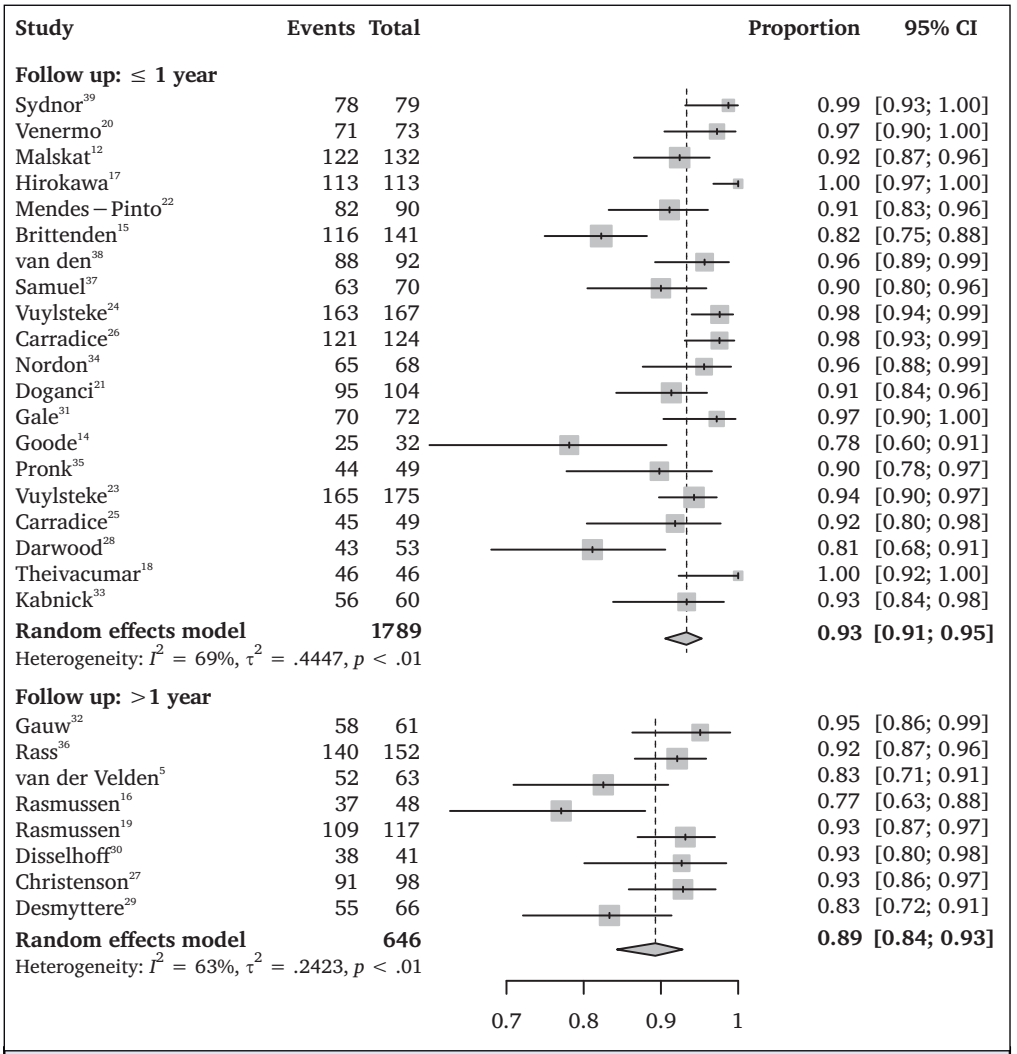

Figure 5. Analysis of follow up subgroups in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies with follow up time ≤ 1 year or > 1 year (93% and 89%, respectively).

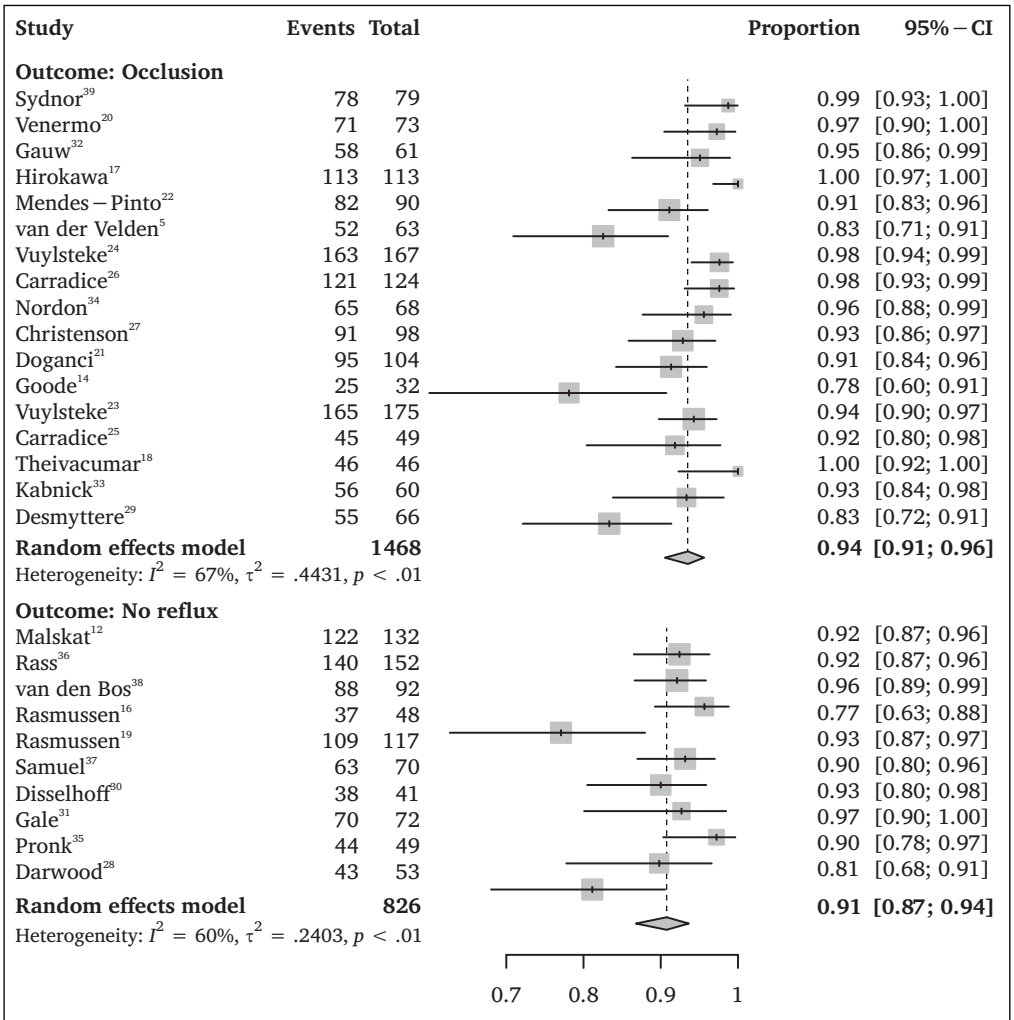

Figure 6. Analysis of outcome subgroups in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies with outcome of occlusion or no reflux (94% and 91%, respectively).

Quality of the studies. Seven manuscripts were classified as studies with a high risk of bias,[15,16,23,28–31] two studies had an unclear risk of bias[18,35] and 19 studies had a low risk of bias[5,12,14,17,19–22,24–27,32–34,36–39] (Fig. 7). Subgroup analysis showed that studies with a low risk of bias had a significantly higher success rate than the studies with a high or unclear risk of bias (93% [95% CI 90–95%] vs. 89% [95% CI 83–93%], $p = .04$). However, in the multivariable meta-regression analysis, no significant difference was detected ($p = .43$).

Sensitivity analysis

Administered amount of energy. Two studies were excluded from this analysis, as the administered energy was unknown.[19,29] In 23 studies, > 40 J/cm were administered during EVLA,[5,14–18,20,21,23–26,28,30–39] in comparison with three studies with an administered energy of ≤40 J/cm[12,22,27] (Fig. 8). There were no significant differences in success rates between these two groups (93% [95% CI 80–95%] vs. 92% [95% CI 89–95%], $p = .43$).

Follow up. Eight studies had a follow up of <1 year,[14,15,17,18,21,23,34,39] 14 studies had a follow up of 1–3 years,[12,20,22,24–29,31,33,35,37,38] and six studies a follow up of ≥3 years[5,16,19,30,32,36] (Fig. 9). There were no significant differences in success rates between these three groups (93% [95% CI 87–97%], 93% [95% CI 90–95%], and 90% [95% CI 83–94%], respectively, $p = .82$).

Publication bias

An alternative funnel plot was constructed and visually inspected (Fig. 10). There appeared to be a low chance of publication bias.

DISCUSSION

This pooled analysis showed an overall success rate of EVLA in GSVs of 92% independent of wavelength, administered amount of energy, duration of follow up, and definition of outcome (occlusion/absence of reflux).

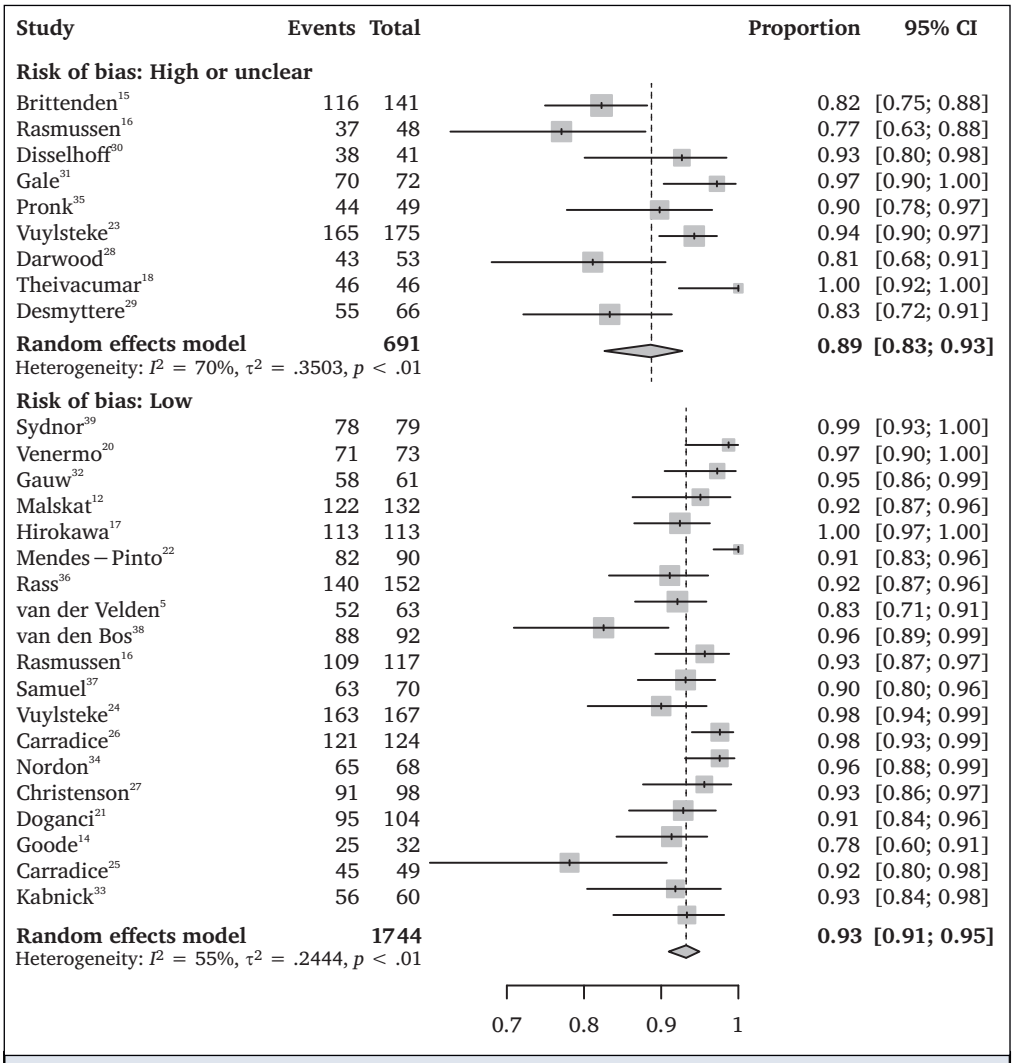

Figure 7. Analysis of bias subgroups in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies with high or unclear, or low risk of bias (89% and 93%, respectively).

The reported overall success rate is in accordance with available systematic reviews reporting on EVLA.[40–43] No difference in EVLA efficacy was expected between Hb target (810, 940, and 980 nm) and water target (1470, 1500, and 1920 nm) wavelengths, as Hb target and water target EVLA devices have been shown to have similar temperature profiles in an experimental setting.[44] Also, a RCT comparing short and long EVLA wavelengths, with equal amount of applied energy, showed comparable efficacy rates of both devices.[12] However, there seem to be differences in patient reported outcomes, favouring longer wavelengths.[12]

According to the findings, it seems that higher administered amount of energy does not benefit the short or long-term success rates of EVLA, in spite of what may have been suggested in previous clinical studies.[9,11,45] In the current meta-analysis, studies with energy levels < 50 J/cm, often suggested as the threshold for successful EVLA, did not have lower success rates than the other studies, indicating that it may be too high. Obviously, a certain amount of energy is needed to generate a sufficient temperature for tissue damage resulting in vein closure, but the exact threshold is unclear. In a study by Mendes-Pinto[22], application of 17.8 J/cm (mean) resulted in a significantly lower EVLA success rate than 24.7 J/cm (88% vs. 95%), indicating that the threshold may be somewhere around these values.

In terms of follow up, it may seem reasonable that a longer follow up period results in lower success rates. However, in this meta-analysis no significant decline in EVLA efficacy (GSV occlusion or absence of reflux) was demonstrated over time. A possible hypothesis is that with increasing follow up period, the treated GSV will not have recurrent reflux, but there will be neovascularisation or reflux at the saphenofemoral junction or accessory anterior saphenous vein.[5] To further investigate this hypothesis,

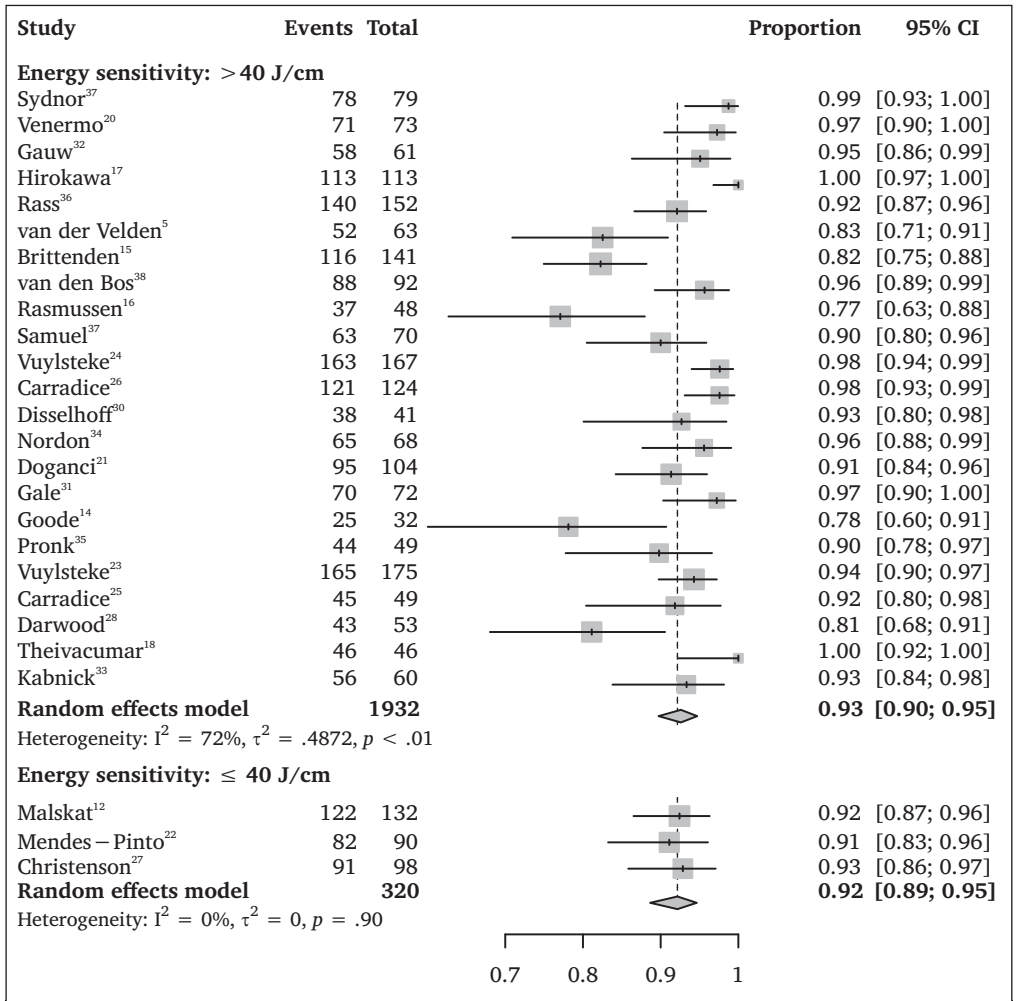

Figure 8. Analysis of energy sensitivity in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies with energy sensitivity of >40 J/cm or ≤ 40 J/cm (93% and 92%, respectively).

further EVLA research is mandatory, with alteration of outcome definitions.

Harmonisation of outcomes is pivotal in clinical research and facilitates pooled analyses. More stringent definitions of "success" such as occlusion are likely to result in lower success rates. However, in this meta-analysis variations of outcome definitions did not influence EVLA success rates. A possible explanation is that the majority of patients treated with EVLA will have GSV occlusion after treatment, and only a small proportion will have absence of reflux. In the present authors' opinion, supported by this study, there is no clinically relevant difference between these two definitions.

EVLA fibre tips were not studied in this meta-analysis on ELVA efficacy, as no difference in ELVA efficacy between different types of fibre tip has been detected in previous RCTs.[17,21,24] The main difference between treatment with diverse EVLA fibres is the difference in post-operative patient reported outcomes, such as pain, satisfaction, and minor complications such as ecchymoses, cutaneous hyperpigmentation, and erythema, possibly related to direct contact with the vein wall (for instance bare fibre vs. radial or tulip tip fibre).[17,21,24]

Limitations to consider when interpreting the present results include the relatively high heterogeneity and inclusion of studies with a high or unclear risk of bias. Despite including only studies with at least three months of follow up, where DUS was used for measuring the outcome, the heterogeneity in the main analysis was relatively high (I^2 = 68%). Differences in wavelength, energy, follow up, and outcome definition could not explain this diversity. The subgroup of studies with low risk of bias showed a higher success rate and less heterogeneity compared with high/unclear risk of bias studies. The difference in success rate was not statistically significant in the multivariable model, because of the distribution of other variables associated with success rate or a loss of power. Sensitivity analysis using other cutoff values for defining the subgroups confirmed the results from the main analyses.

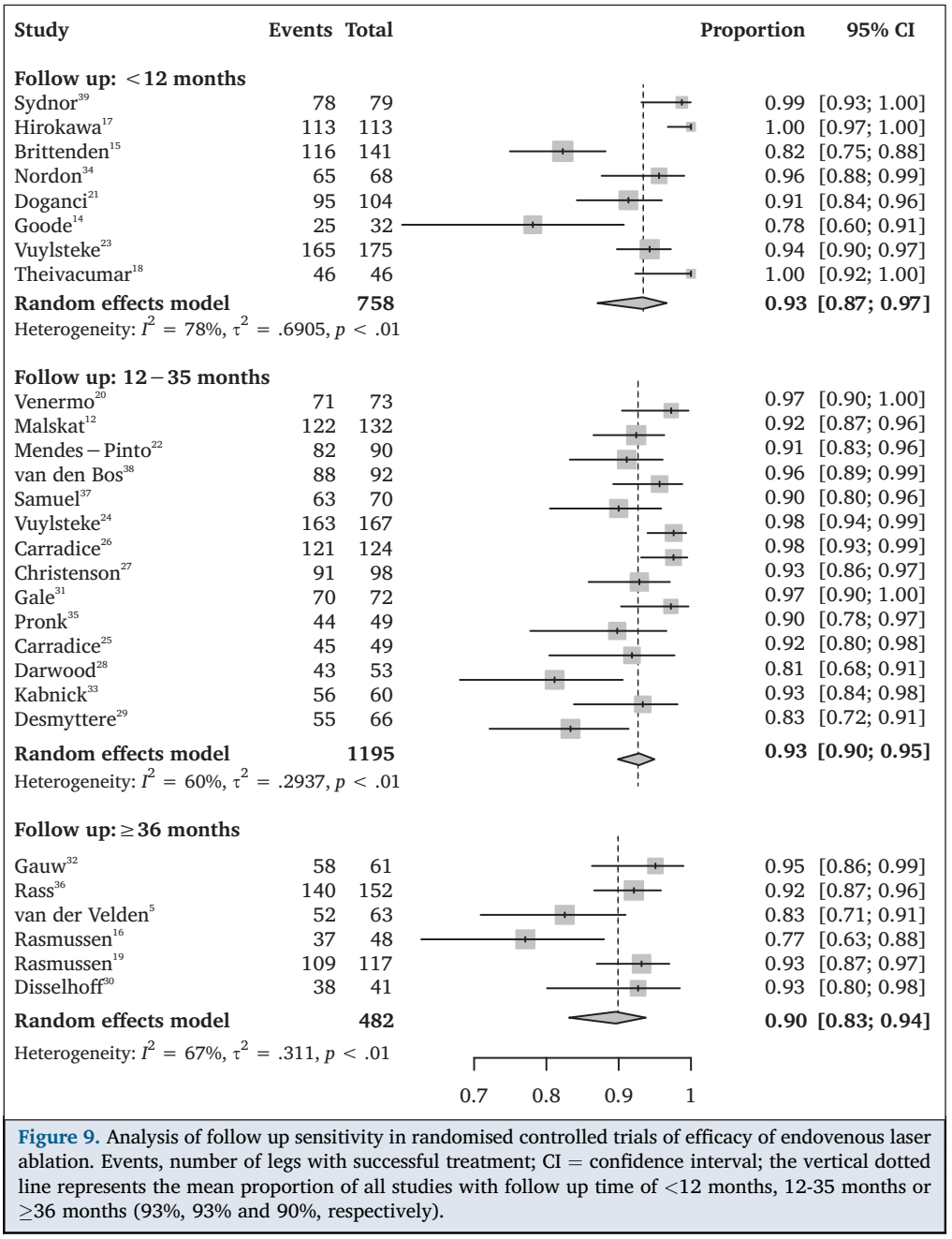

Figure 9. Analysis of follow up sensitivity in randomised controlled trials of efficacy of endovenous laser ablation. Events, number of legs with successful treatment; CI = confidence interval; the vertical dotted line represents the mean proportion of all studies with follow up time of <12 months, 12-35 months or ≥36 months (93%, 93% and 90%, respectively).

A major strength of this systematic review is that only RCTs were included; they are the highest form of evidence for therapeutic studies. Consequently, the included studies were generally homogeneous, in contrast to other meta-analyses including different study types.

It seems that EVLA treatment is effective in many settings and wavelengths. However, it is proven that longer wavelengths (for instance 1470 nm) induce less post-operative pain[12] and therefore may be preferred. Also, it is reasonable to use a functional power setting (for instance 10 W) and administer ≥ 30 J/cm energy to get the intended anatomical effect.

Attention in research and daily practice seems to be shifting from efficacy to clinically relevant outcomes. In the present authors' opinion, patient reported outcomes and symptoms should be the primary study outcome in future research on EVLA efficacy to find the most patient friendly EVLA setting, next to neovascularisation or recurrent varicose veins as secondary outcome,[5] rather than ST occlusion or absence of reflux. This first meta-analysis on EVLA alone, has demonstrated that different kinds of EVLA settings and devices are effective in resolving GSV incompetence, and that treated GSVs do generally not re-open after successful treatment.

In conclusion, the EVLA wavelengths, administered energy, and definitions of outcome that have been studied clinically, have no influence on the treatment success rate of EVLA. The overall success rate of EVLA is proven to be

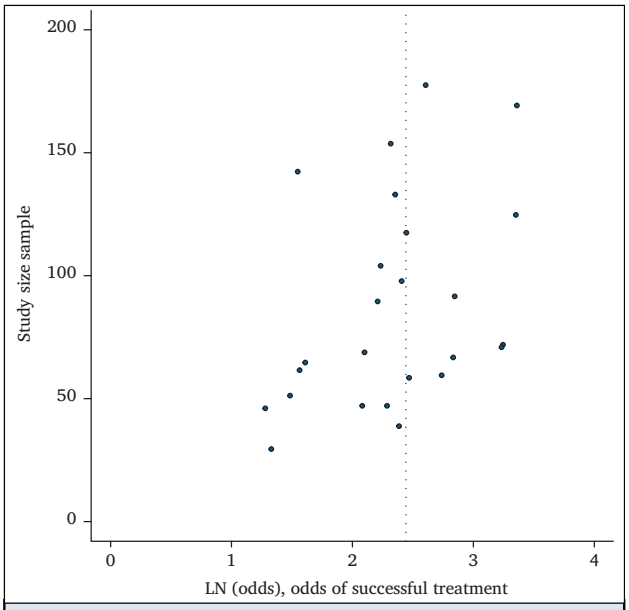

Figure 10. Alternative funnel plot. LN = natural log.

high (92%), confirming that EVLA is a highly effective treatment for incompetent GSVs, also with increasing follow up.

CONFLICT OF INTEREST

None.

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None.

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APPENDIX.

Full electronic search strategy

Time period: all articles up until the November 2017

Search criteria (Medline Epub (Ovid)): (exp "Varicose Veins"/OR (varic* OR varix).ab,ti. OR (("Saphenous Vein"/OR (vein OR vena OR venous OR saphen*).ab,ti.) AND (exp "Peripheral Vascular Diseases"/OR exp "Venous Insufficiency"/OR (insuffic* OR diseas* OR dilat*).ab,ti.))) AND (exp "Laser Therapy"/OR "Lasers/therapeutic use" OR (((endoven* OR ((endo OR intra) ADJ (venous OR vascular)) OR endovascular OR intraven* OR intravascular OR EVA OR EVTA) AND laser) OR evla OR evlt).ab,ti.) NOT (animals NOT humans).sh.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2018.10.036.

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