EVLA parameters do not influence efficacy – results of a systematic review and meta-analysis

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Submitted

ABSTRACT

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

Methods: A systematic review was performed of RCTs with follow-up of more than three months. 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 analysis and metaregression analysis included wavelengths (short (810, 940 and 980 nm), long (1470, 1500 and 1920 nm)) amount of energy (≤50 J/cm, >50 J/cm), follow-up (≤ 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 2,829 GSVs were included. 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%) versus 92% (95% CI 89-94%), p = 0.15), high or low administered energy (93% (95% CI 89-95%) versus 92% (95% CI 90-94%), p = 0.99), long or short follow-up (89% (95% CI 84-93%) versus 93% (95% CI 91-95%), p = 0.13) and outcome definition (occlusion group 94% (95% CI 91-96%) versus absence of reflux group 91% (95% CI 87-94%), p = 0.26). Studies with low risk of bias had a significantly higher success rate than high or unclear risk of bias (93% (95% CI 90-95%) versus 89% (95% CI 83-93%), p = 0.04).

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

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 choice of treatment 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 standardized procedure, and can be used in many different settings. As the years pass by, evidence of long-term follow-up from well-designed randomized controlled trials becomes more and more available and also the variation in EVLA devices and settings increases. The working mechanism of EVLA is not exactly known but is mainly based on heat transfer from the EVLA fiber tip to surrounding tissue. There are some known mechanisms by which the hot fiber tip may transfer heat to the vein wall; direct contact, heat conduction, and generation of steam bubbles (6). Although the focus 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 amount of energy and follow-up period have never been properly explored in a systematic review and pooled analyses. In the current maze of available options, it remains an important question if there are optimal effective EVLA devices or (power) settings, in terms of short and long-term efficacy. The objective of the present meta-analysis was to systematically review and summarize the available randomized controlled trials of EVLA efficacy and define the differences in success rate of variation in wavelength, administered energy, outcome definition and follow-up period.

METHODS

Literature search

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

Inclusion criteria

In this meta-analysis, only randomized controlled trials (RCTs) regarding 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 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, since this approach may have influenced the outcome measures. Trials about 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 period 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 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 used EVLA wavelength(s), the administered energy, the duration of follow-up, the US outcome definition, the number of treated GSVs available at end of follow-up and success rate at end of follow-up were extracted. Extensive quality assessment of the studies was performed, according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (7).

Statistical analysis

The primary outcome was the proportion of successful treatment (occlusion or no reflux) at 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 I^2 was calculated and represents the amount of total variance explained by genuine differences between the studies (heterogeneity) rather than by chance due to sampling error (homogeneity). Metaregression was performed to identify the possible source of heterogeneity and the model included quality of the study (low or unclear/high risk of bias) (7), 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 (8)), 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; we expected that low quality of the study, longer follow-up (9), lower amount of energy (8, 10) used and defining occlusion as outcome (instead of absence of reflux) may result in lower success rate, differences between wavelengths were not expected (11). Subgroup analysis were 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 metaregression was used in which a two-sided p-value <0.05 indicated a statistical significance. Studies with missing values of subgroup variables were excluded from the univariable metaregression. The multivariable metaregression included all studies by 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 if lower energy is still effective, and to differentiate between short, intermediate and long follow-up period.

In order to detect possible publication bias a funnel plot was constructed. For low and high proportional outcomes, traditional funnel plots (log odds vs 1/SE) can result in funnelplot asymmetry without publication bias (12). Therefore, an alternative funnelplot (sample size vs log odds) was constructed and visually inspected. Currently there are no suitable statistical test for funnel plot asymmetry for proportion meta-analysis (12).

This review was conducted and reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA)(13).

RESULTS

Study selection and characteristics

The search yielded a total of 4,567 articles (Figure 1). After reduplication 2,807 articles remained. We identified 91 eligible studies after 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 Table 1. In the 28 studies, a total of 2,829 GSVs were included. The study size sample varied from 39 (14) to 212 (15) GSVs.

Quality of the studies/bias assessment

We assessed the risk of bias of the included 28 articles as having low, unclear or high risk of bias (Table 2). In most included RCTs, study treatments were technically too different, which made blinding of either physicians, patients or assessors impossible. Therefore, studies where no blinding was applied could still be categorized as low risk of bias in the present meta-analysis. The main reasons of assessing a study as high risk of bias were reported missing outcome of more than 30% of the study population and/or unclear procedure of randomization.

Success rate

The pooled anatomical success rates are shown in Figure 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).

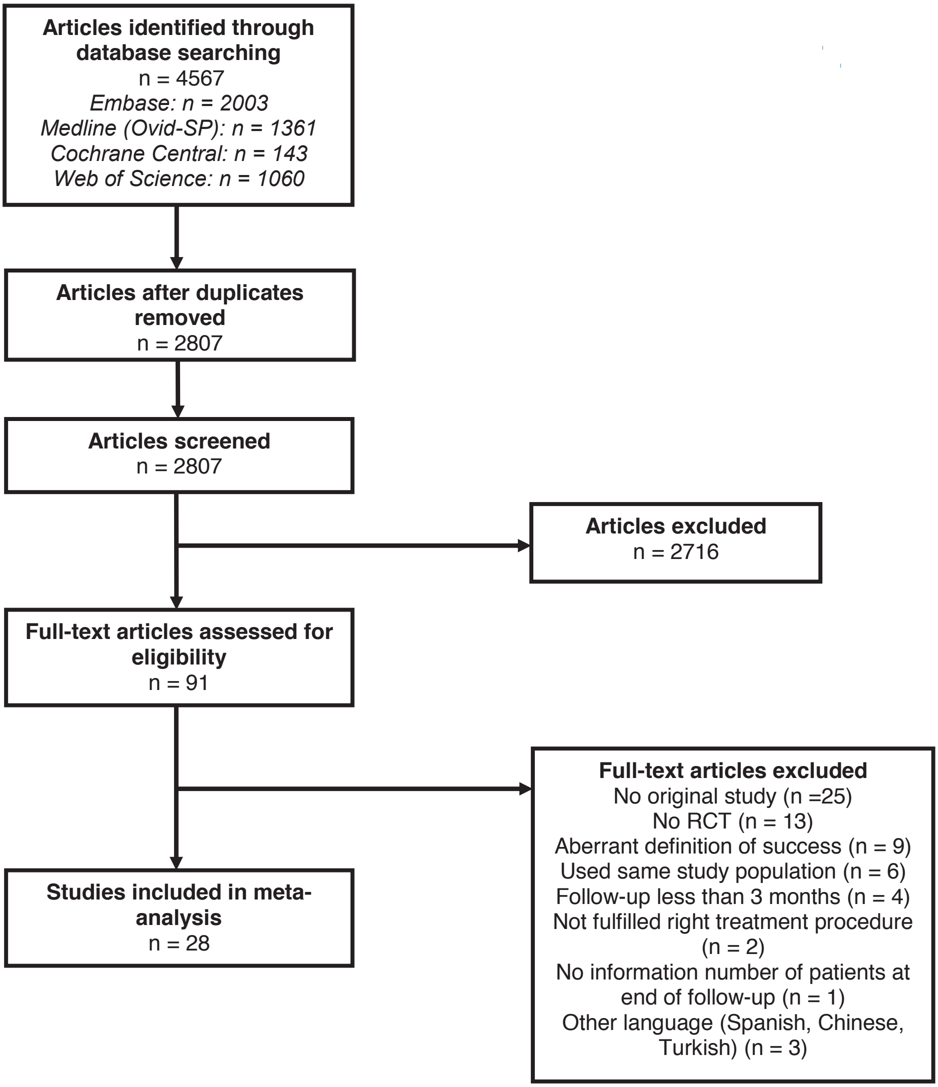

Figure 1. Flow chart of search strategy and study selection

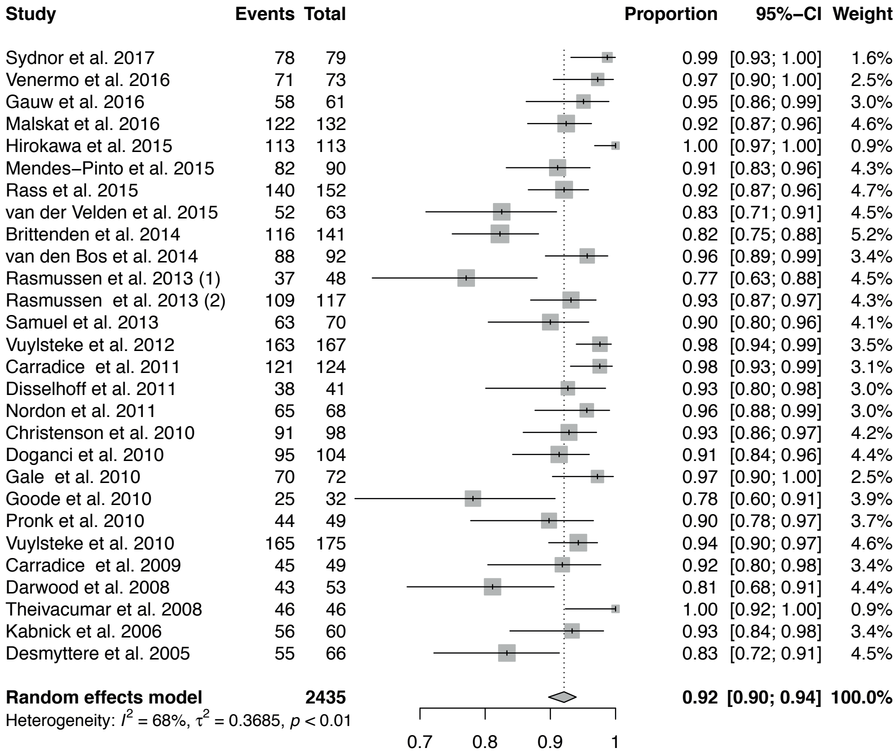

Figure 2. Overall EVLA treatment success

Metaregression and subgroup analysis

The results of uni- and multivariable metaregression analysis are summarized in Table 3. The outcomes of the univariable metaregression 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, since 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 (11, 17, 21-24), and with short wavelengths (810, 940 and 980 nm) in (at least) one group in 23 studies (5, 11, 14, 16-18, 21, 23, 25-38) (Figure 3). The success rates of long and short EVLA wavelengths were not significantly different; 95% (95% CI 91-97%) versus 92% (95% CI 89-94%), p = 0.15.

Administered amount of energy

Of two studies, the administered amount of energy during treatment was unknown (19, 29). In 20 studies, more than 50 J/cm was administered during EVLA (5, 14-18, 20, 21,

Table 1. Study characteristics

Study label	Authors	Year	Country	Study type	No included GSVs	Wavelength(s)	Administered energy (presented in study)	Follow-up (months)	No GSVs end of follow-up	Definition success	Success rate
Sydnor_2017 (39)	Sydnor et al.	2017	USA	RCT	100	980	50-80	6	79	occlusion	99%
Venermo_2016 (20)	Venermo et al.	2016	Finland	RCT	73	980, 1470	70	12	73	occlusion	97%
Gauw_2016 (32)	Gauw et al.	2016	Netherlands	RCT	62	980	65	62	61	occlusion	95%
Malskat_2016 (11)	Malskat et al.	2016	Netherlands	RCT	142	940; 1470	40	12	132	no reflux	91%; 94%
Hirokawa_2015 (17)	Hirokawa et al.	2015	Japan	RCT	113	980; 1470	70-85	3	113	occlusion	100%; 100%
Mendes-Pinto_2015 (22)	Mendes-Pinto et al.	2015	Brazil	RCT	90	1470; 1920	25; 18	12	90	occlusion	95%; 88%
Rass_2015 (36)	Rass et al.	2015	Germany	RCT	185	810	50	62	152	no reflux	92%
van der Velden_2015 (5)	van der Velden et al.	2015	Netherlands	RCT	80	940	60	62	63	occlusion	83%
Brittenden_2014 (15)	Brittenden et al.	2014	UK	RCT	212	unknown	83	6	141	both	82%
van den Bos_2014 (40)	van den Bos et al.	2014	Netherlands	RCT	110	940	60	12	92	no reflux	96%
Rasmussen_2013 (1) (16)	Rasmussen et al.	2013	Denmark	RCT	69	980	74	62	48	no reflux	77%
Rasmussen_2013 (2) (19)	Rasmussen et al.	2013	Denmark	RCT	144	980, 1470	unknown	36	117	no reflux	93%
Samuel_2013 (37)	Samuel et al.	2013	UK	RCT	76	810	60-70	12	70	no reflux	90%
Vuylsteke_2012 (24)	Vuylsteke et al.	2012	Belgium	RCT	174	1470	60	12	167	occlusion	98%
Carradice_2011 (26)	Carradice et al.	2011	UK	RCT	139	810	95	12	124	occlusion	98%
Disselhoff_2011 (30)	Disselhof et al.	2011	Netherlands	RCT	60	810	57	62	41	no reflux	93%
Nordon_2011 (34)	Nordon et al.	2011	UK	RCT	80	810	80	3	68	occlusion	96%

Table 1. Study characteristics (continued)

Study label	Authors	Year	Country	Study type	No included GSVs	Wavelength(s)	Administered energy (presented in study)	Follow-up (months)	No GSVs end of follow-up	Definition success	Success rate
Christenson_2010 (27)	Christenson et al.	2010	Switzerland	RCT	100	980	40	24	98	occlusion	93%
Doganci_2010 (21)	Doganci et al.	2010	Turkey	RCT	106	980; 1470	90	6	106	occlusion	100%; 100%
Gale_2010 (31)	Gale et al.	2010	USA	RCT	72	810	92	12	72	no reflux	97%
Goode_2010 (14)	Goode et al.	2010	UK	RCT	39	810	80	9	32	occlusion	78%
Pronk_2010 (35)	Pronk et al.	2010	Netherlands	RCT	62	980	65	12	49	no reflux	90%
Vuylsteke_2010 (23)	Vuylsteke et al.	2010	Belgium	RCT	180	980; 1500	72; 49	6	175	occlusion	96%; 93%
Carradice_2009 (25)	Carradice et al.	2009	UK	RCT	50	810	80-100	12	49	occlusion	92%
Darwood_2008 (28)	Darwood et al.	2008	UK	RCT	79	810	61	12	53	no reflux	81%
Theivacumar_2008 (18)	Theivacumar et al.	2008	UK	RCT	46	810	60-70	3	46	occlusion	100%
Kabnick_2006 (33)	Kabnick et al.	2006	USA	RCT	60	810, 980	50	12	60	occlusion	93%
Desmyttere_2005 (29)	Desmyttere et al.	2005	France	RCT	126	980	unknown	24	66	occlusion	83%

Table 2. Bias assessment

Study	Year	Random assignment	Foresee assignment	Group similarity	Blinding patients	Blinding doctors	Blind assessors	Missings	Reporting bias	Other bias	Overall assessment
Sydnor	2017	-	-	-	-	+	+	-	-	-	-
Venermo	2017	-	-	-	+	+	?	-	-	-	-
Gauw	2016	-	-	-	+	+	+	-	-	-	-
Malskat	2016	-	-	-	+	+	+	-	-	-	-
Hirakowa	2015	-	-	-	+	+	+	-	-	-	-
Mendes	2015	-	-	-	+	+	+	-	-	-	-
Rass	2016	-	-	-	+	+	+	-	-	-	-
vd Velden	2015	-	-	-	+	+	+	-	-	-	-
Brittenden	2014	-	-	-	+	+	+	+	-	-	+
van den Bos	2014	-	-	-	+	+	+	-	-	-	-
Rasmussen (1)	2013	-	-	-	+	+	+	+	-	-	+
Rasmussen (2)	2013	-	-	-	+	+	+	-	-	-	-
Samuel	2013	-	-	-	+	-	+	-	-	-	-
Vuylsteke	2012	-	-	-	+	+	+	-	-	-	-
Carradice	2011	-	-	-	+	+	+	-	-	-	-
Disselhoff	2011	-	-	-	+	+	+	+	-	-	+
Nordon	2011	-	-	-	-	+	-	-	-	-	-
Christenson	2010	-	-	-	+	+	+	-	-	-	-
Doganci	2010	-	-	-	+	+	+	-	-	-	-
Gale	2010	-	+	-	+	+	+	-	-	-	+
Goode	2010	-	-	-	-	+	+	-	-	-	-
Pronk	2010	-	?	-	+	+	+	-	-	-	?
Vuylsteke	2010	-	+	-	+	+	+	-	-	-	+
Carradice	2009	-	-	-	+	+	+	-	-	-	-
Darwood	2008	?	+	-	+	+	+	-	-	-	+
Theivacumar	2008	-	?	-	+	+	+	-	-	-	?
Kabnick	2006	-	-	-	-	-	+	-	-	-	-
Desmyttere	2005	-	-	-	+	+	+	+	-	-	+

High risk of bias	+
Low risk of bias	-
Unclear risk of bias	?

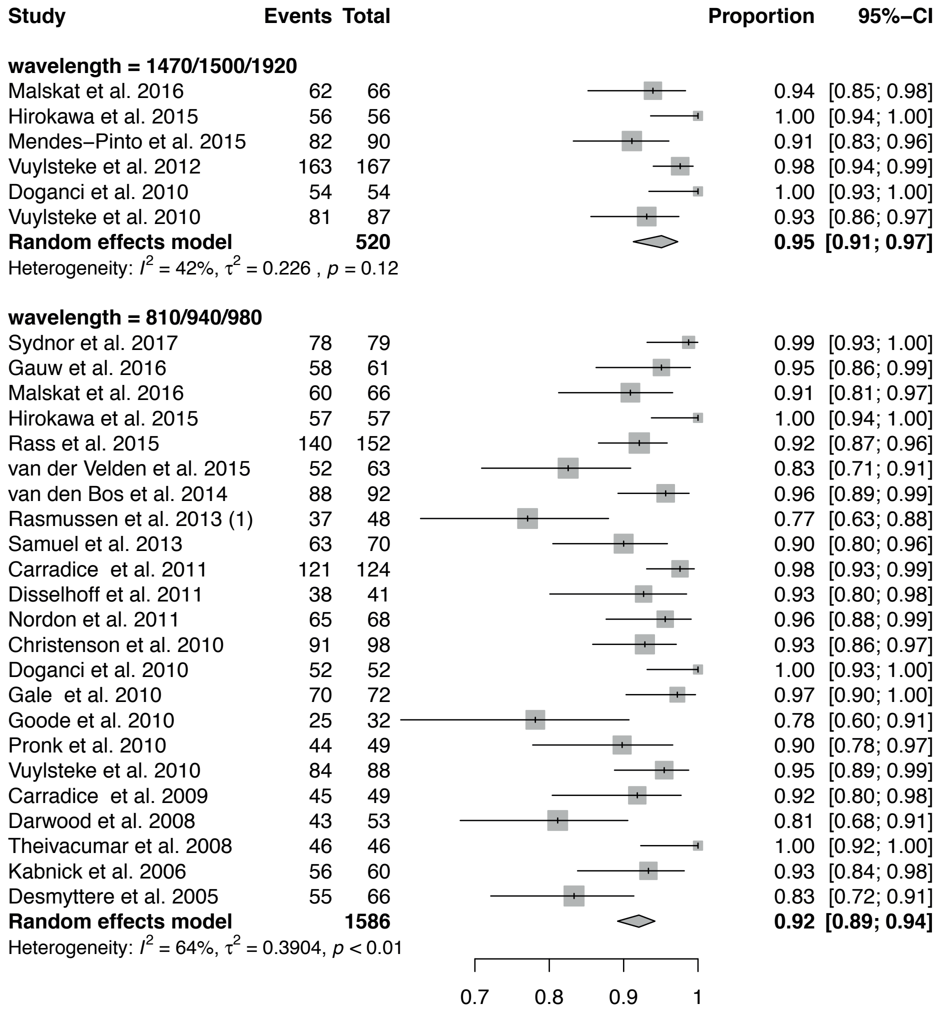

Figure 3. Wavelength subgroup analysis

24-26, 28, 30-32, 34, 35, 37, 39) in comparison to five studies with a administered energy of 50 J/cm or less (11, 22, 27, 33, 36) (Figure 4). There were no significant differences in success rates between these two groups; 93% (95% CI 89-95%) versus 92% (95% CI 90-94%), p = 0.99.

Follow-up

The mean follow-up period of all studies was 20,7 months. The maximum period of follow-up was 62 months. Eight studies had a follow-up of more than one year (5, 16, 19, 27, 29, 30, 32, 36), 20 studies of up to one year (11, 14, 15, 17, 18, 20-26, 28, 31, 33-35, 37-39) (Figure 5). Follow-up of >1 year did not correlate with a statistical significant

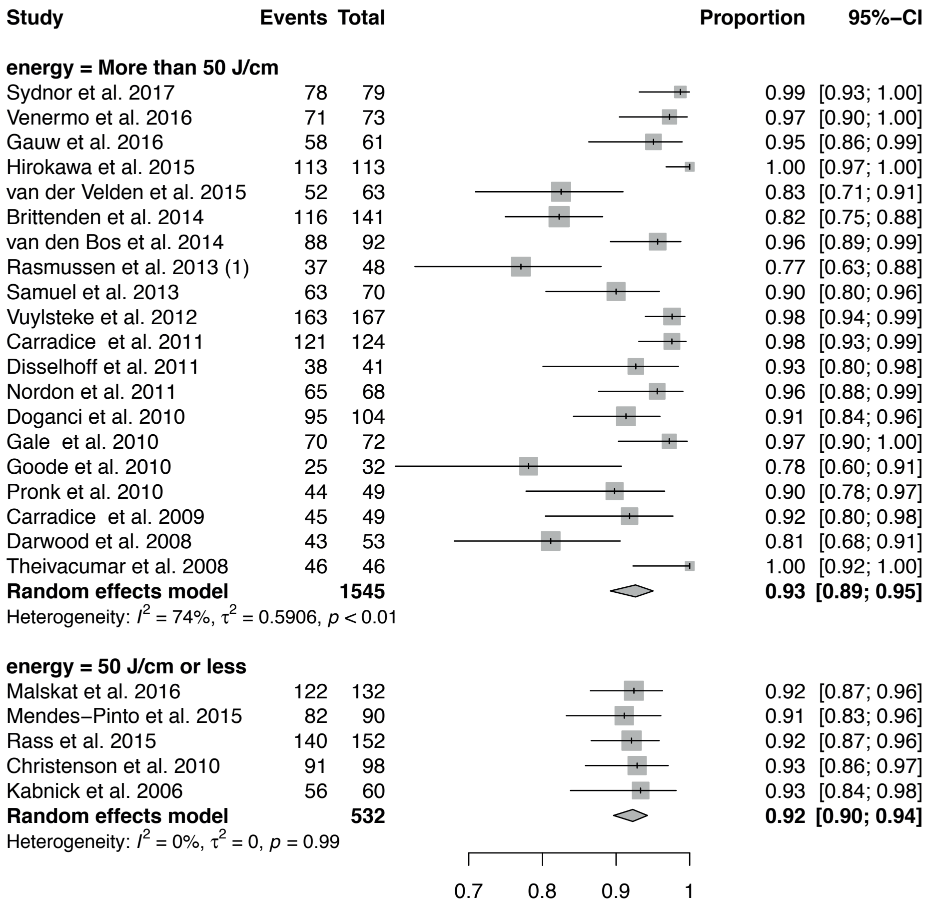

Figure 4. Energy subgroup analysis

lower success rate than ≤1 year; 89% (95% CI 84-93%) versus 93% (95% CI 91-95%), p = 0.13, respectively.

Definition of outcome

One study (15) was excluded from this subgroup analysis, since 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 (11, 16, 19, 28, 30, 31, 35-38) (Figure 6). There was no statistically significant difference between these two outcome definitions; 94% (95% CI 91-96%) in the occlusion group versus 91% (95% CI 87-94%) in the absence of reflux group, p = 0.26.

Table 3. Metaregression

Study characteristic	Number of studies	Reference numbers	Pooled proportion of anatomical success	I^2	p-value univariable metaregression*	p-value multivariable metaregression#
Wavelength					0.15	0.66
Long	6	11, 17, 21-24	0.9509 [0.9130; 0.9728]	42.3%		
Short	23	5, 11, 14, 16-18, 21, 23, 25-38	0.9205 [0.8919; 0.9421]	63.6%		
Energy					0.99	0.76
<= 50 J/cm	5	11, 22, 27, 33, 36	0.9227 [0.8967; 0.9426]	0.0%		
>50 J/cm	20	5, 14-18, 20, 21, 24-26, 28, 30-32, 34, 35, 37, 39	0.9264 [0.8923; 0.9503]	73.8%		
Follow up					0.13	0.27
<= 1 year	20	11, 14, 15, 17, 18, 20-26, 28, 31, 33-35, 37-39	0.9330 [0.9055; 0.9529]	69.4%		
> 1 year	8	5, 16, 19, 27, 29, 30, 32, 36	0.8927 [0.8430; 0.9281]	63.0%		
Outcome definition					0.25	0.37
Occlusion	18	5, 14, 17, 18, 20-27, 29, 32-34, 39	0.9353 [0.9055; 0.9561]	66.7%		
No reflux	10	11, 16, 19, 28, 30, 31, 35-38	0.9076 [0.8680; 0.9363]	59.9%		
Risk of bias					0.04	0.43
Low	19	5, 11, 14, 17, 19-22, 24-27, 32-34, 36-39	0.9324 [0.9098; 0.9496]	55.3%		
High or unclear	9	15, 16, 18, 23, 28-31, 35	0.8863 [0.8266; 0.9273]	70.2%		

*Only studies with non-missing variables were included in the analysis; #Also studies with unknown variables were included in the analysis

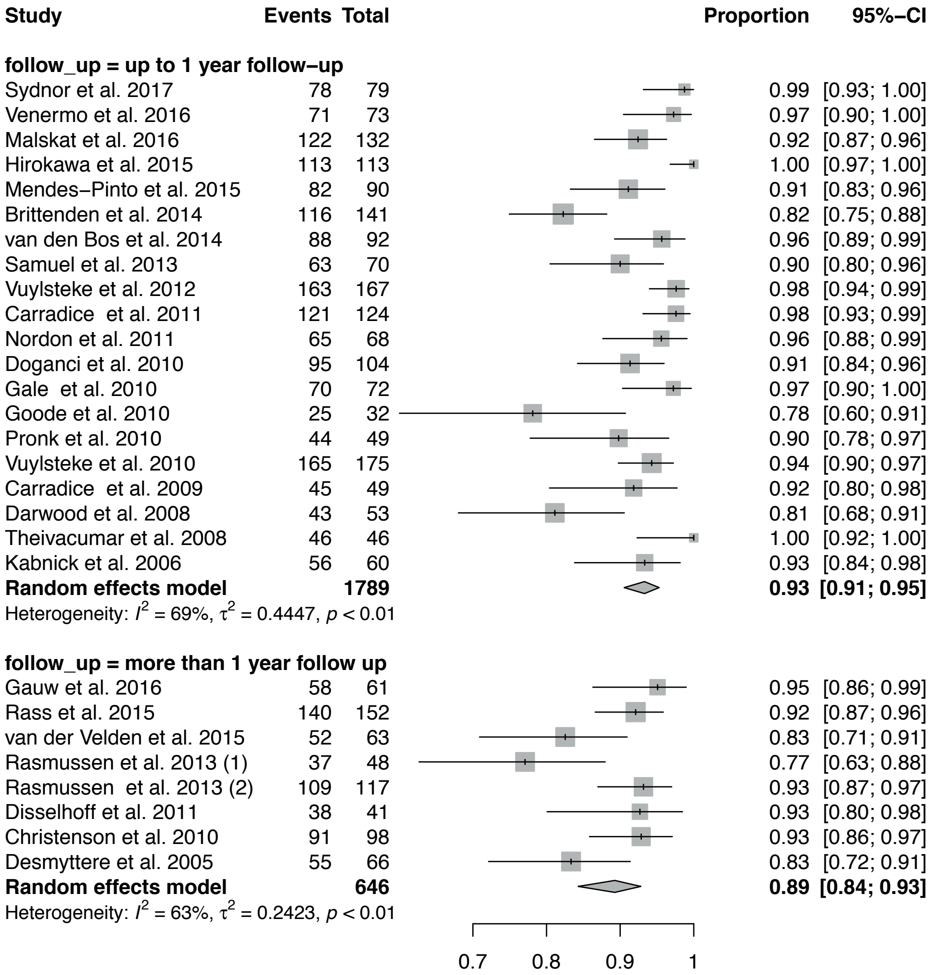

Figure 5. Follow-up subgroup analysis

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, 11, 14, 17, 19-22, 24-27, 32-34, 36-39) (Figure 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%) versus 89% (95% CI 83-93%), p = 0.04. However, in the multivariable metaregression analysis, no significant difference was detected; p = 0.43.

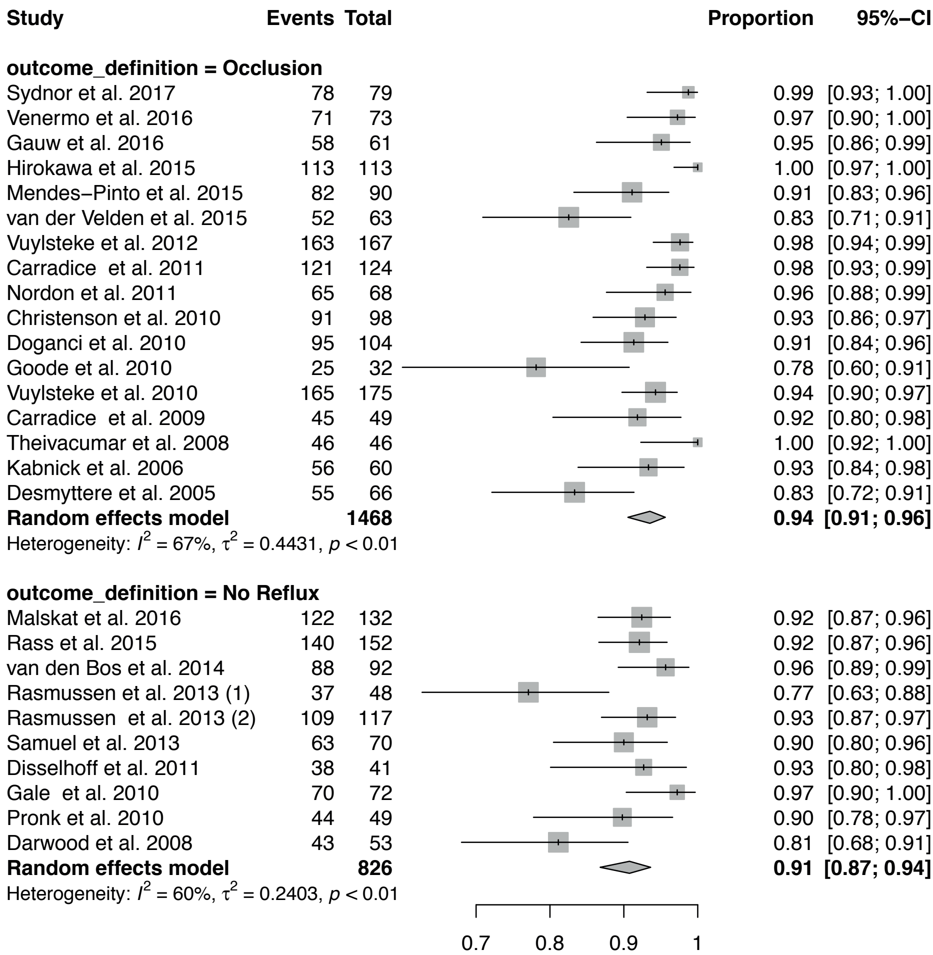

Figure 6. Outcome definition subgroup analysis

Sensitivity analysis

Administered amount of energy

Two studies were excluded from this analysis, since the administered energy was unknown (19, 29). In 23 studies, more than 40 J/cm were administered during EVLA (5, 14-18, 20, 21, 23-26, 28, 30-39) in comparison to three studies with an administered energy of 40 J/cm or less (11, 22, 27) (Figure 8). There were no significant differences in success rates between these two groups; 93% (95% CI 80-95%) versus 92% (95% CI 89-95%), p = 0.43.

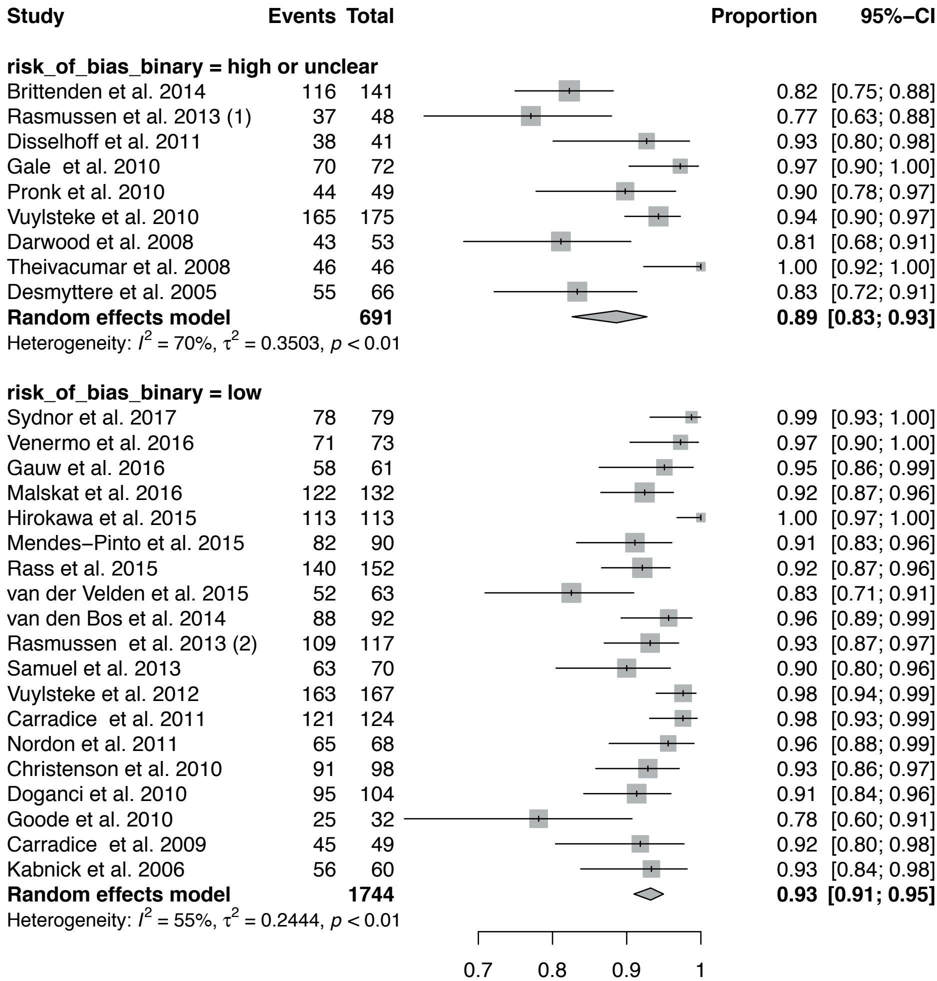

Figure 7. Bias subgroup analysis

Follow-up

Eight studies had a follow-up of less than one year (14, 15, 17, 18, 21, 23, 34, 39), 14 studies of one to three years (11, 20, 22, 24-29, 31, 33, 35, 37, 38) and six studies of three years or more (5, 16, 19, 30, 32, 36) (Figure 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 = 0.82.

Publication bias

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

Study	Events	Total	Proportion	95%–CI
energy_sens = More than 40 J/cm				
Sydnor et al. 2017	78	79	0.99	[0.93; 1.00]
Venermo et al. 2016	71	73	0.97	[0.90; 1.00]
Gauw et al. 2016	58	61	0.95	[0.86; 0.99]
Hirokawa et al. 2015	113	113	1.00	[0.97; 1.00]
Rass et al. 2015	140	152	0.92	[0.87; 0.96]
van der Velden et al. 2015	52	63	0.83	[0.71; 0.91]
Brittenden et al. 2014	116	141	0.82	[0.75; 0.88]
van den Bos et al. 2014	88	92	0.96	[0.89; 0.99]
Rasmussen et al. 2013 (1)	37	48	0.77	[0.63; 0.88]
Samuel et al. 2013	63	70	0.90	[0.80; 0.96]
Vuylsteke et al. 2012	163	167	0.98	[0.94; 0.99]
Carradice et al. 2011	121	124	0.98	[0.93; 0.99]
Disselhoff et al. 2011	38	41	0.93	[0.80; 0.98]
Nordon et al. 2011	65	68	0.96	[0.88; 0.99]
Doganci et al. 2010	95	104	0.91	[0.84; 0.96]
Gale et al. 2010	70	72	0.97	[0.90; 1.00]
Goode et al. 2010	25	32	0.78	[0.60; 0.91]
Pronk et al. 2010	44	49	0.90	[0.78; 0.97]
Vuylsteke et al. 2010	165	175	0.94	[0.90; 0.97]
Carradice et al. 2009	45	49	0.92	[0.80; 0.98]
Darwood et al. 2008	43	53	0.81	[0.68; 0.91]
Theivacumar et al. 2008	46	46	1.00	[0.92; 1.00]
Kabnick et al. 2006	56	60	0.93	[0.84; 0.98]
Random effects model		**1932**	**0.93**	**[0.90; 0.95]**
Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.4872$, $p < 0.01$				
energy_sens = 40 J/cm or less				
Malskat et al. 2016	122	132	0.92	[0.87; 0.96]
Mendes–Pinto et al. 2015	82	90	0.91	[0.83; 0.96]
Christenson et al. 2010	91	98	0.93	[0.86; 0.97]
Random effects model		**320**	**0.92**	**[0.89; 0.95]**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.90$				

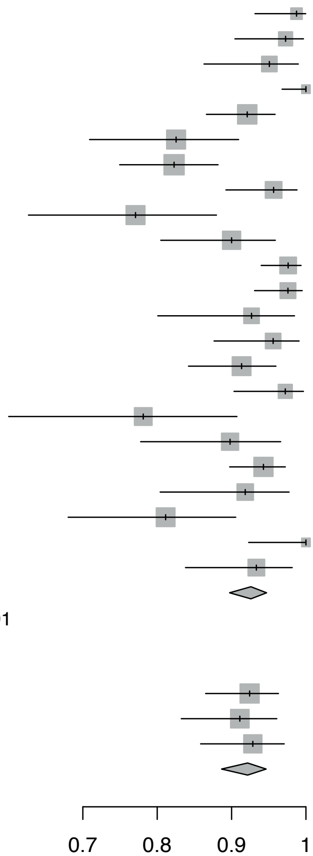

Figure 8. Energy sensitivity analysis

DISCUSSION

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

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, since Hb-target and water-target EVLA devices have 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

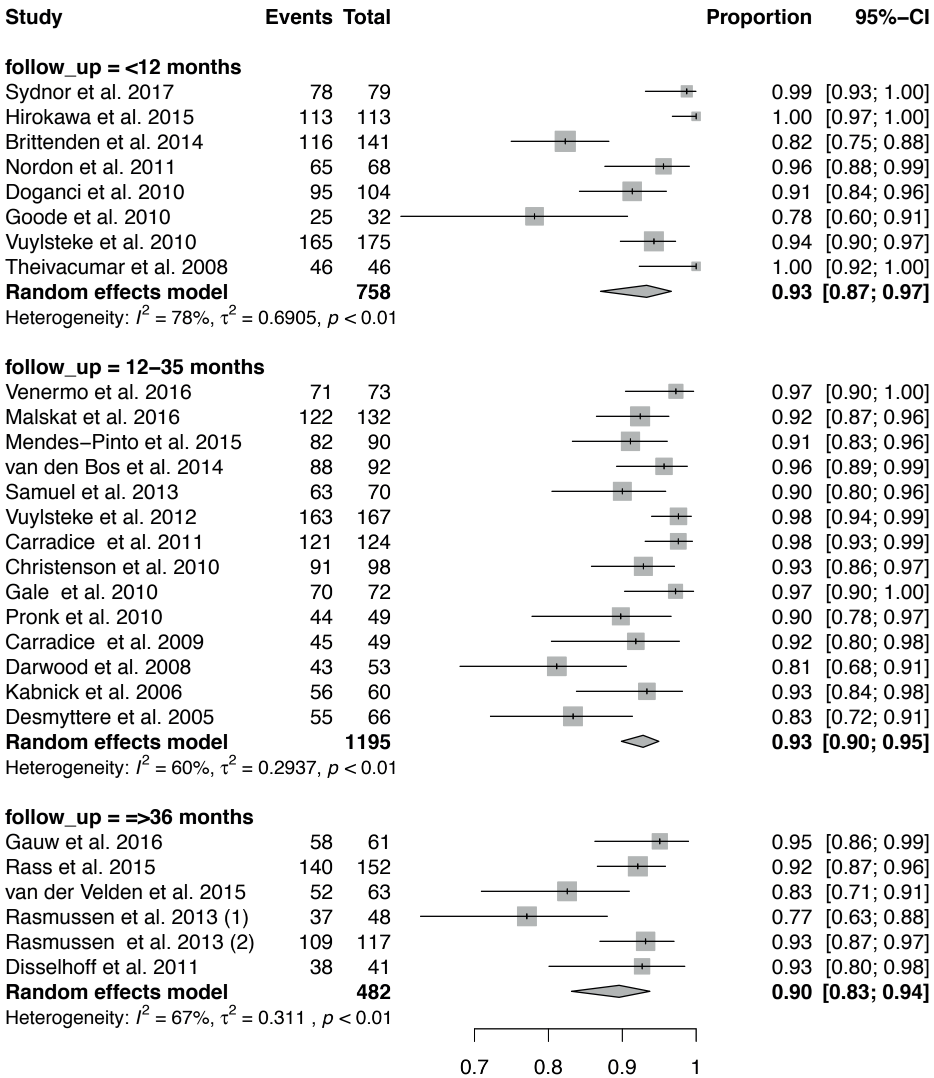

Figure 9. Follow-up sensitivity analysis

both devices (11). However, there seem to be differences in patient reported outcomes, favoring longer wavelengths (11).

According to our 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 (8, 10, 45). In the current meta-analysis, studies with lower energy levels than 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

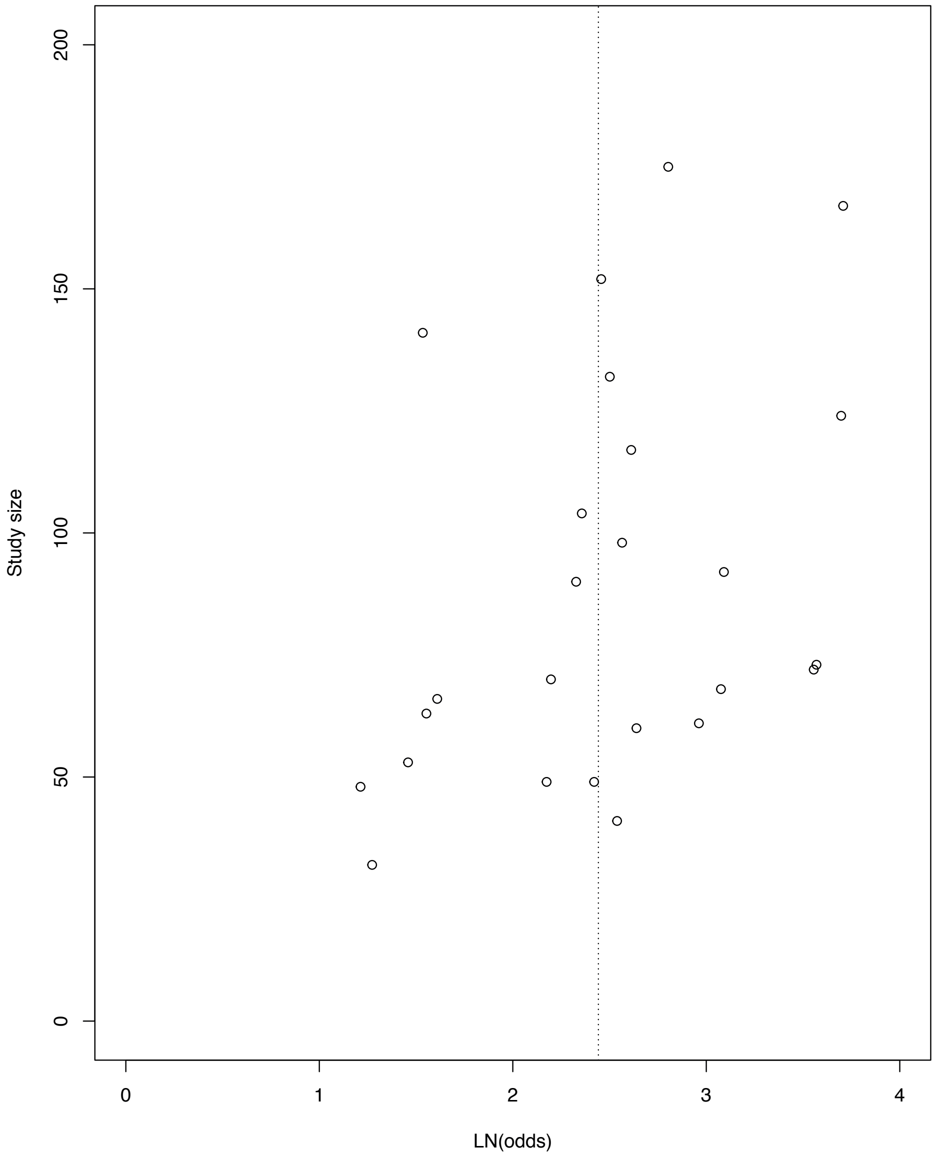

Figure 10. Alternative funnel plot

temperature for tissue damage resulting in vein closure, but it is unclear what the exact threshold is. In a study by Mendes-Pinto, application of 17.8 J/cm (mean) resulted in a significantly lower EVLA success rate than 24.7 J/cm (88% versus 95%), indicating that the threshold may be somewhere around these values.

In terms of follow-up, it may seem reasonable that 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 the years. A possible hypothesis is that with increasing follow-up period, not the treated GSV will have recurrent reflux, but there will be neovascularization or reflux at the saphenofemoral junction or accessory anterior saphenous vein (5). To further investigate this hypothesis, further EVLA research is mandatory, with alteration of outcome definitions.

Harmonization 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 our opinion, supported by this study, there is no clinically relevant difference between these two definitions.

EVLA fiber tips were not studied in this meta-analysis on ELVA efficacy, since no difference in ELVA efficacy between different types of fiber tips was ever detected in previous RCTs (17, 21, 24). The main difference between treatment with diverse EVLA fibers is the difference in postoperative 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 fiber versus radial or tulip tip fiber) (17, 21, 24).

Limitations to consider when interpreting our 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 3 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 to high/unclear risk of bias studies. The difference in success rate was not statistically significant in the multivariable model, due to the distribution of other variables associated with success rate or a loss of power. Sensitivity analysis using other cut-off values for defining the subgroups confirmed the results from the main analyses.

A major strength of this systemic 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-analysis including different study types.

Attention in research and daily practice seems to be shifting from efficacy to clinically relevant outcomes. To our opinion, patient reported outcomes and symptoms should be the primary study outcome in future research on EVLA efficacy in order to find the most patient friendly EVLA setting, next to neovascularization or recurrent varicose veins as secondary outcome (5) instead of ST occlusion or absence of reflux. After all, this first meta-analysis on only EVLA demonstrated that different kinds of EVLA settings and devices are proven to be effective in resolving GSV incompetence, and treated GSVs do not intend to re-open in time once they are successfully treated.

In conclusion, EVLA wavelength, administered energy and definition of outcome have no influence on the treatment success rate of EVLA. The overall success rate of EVLA is proven to be high (92%), confirming that EVLA is a highly effective treatment for incompetent GSVs, also with increasing follow-up period.

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