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REVIEW

A Systematic Review and Meta-analysis of Thrombotic Events Following Endovenous Thermal Ablation of the Great Saphenous Vein

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WHAT THIS PAPER ADDS

The incidence of thrombotic complications following endovenous thermal ablation (EVTA) of varicose veins is uncertain. In this systematic review and meta-analysis, it was found that endovenous heat induced thrombosis, deep venous thrombosis, and PE occur infrequently after great saphenous endothermal ablation. However, given the large numbers of patients that undergo endothermal ablation, there is a need for further research on the natural history, management, and burden of these thrombotic events.

Objectives: A systematic review and meta-analysis was performed to determine the incidence of thrombotic events following great saphenous vein (GSV) endovenous thermal ablation (EVTA).

Methods: MEDLINE, Embase and conference abstracts were searched. Eligible studies were randomised controlled trials and case series that included at least 100 patients who underwent GSV EVTA (laser ablation or radiofrequency ablation [RFA]) with duplex ultrasound (DUS) within 30 days. The systematic review focused on the complications of endovenous heat induced thrombosis (EHIT), deep venous thrombosis (DVT), and pulmonary embolism (PE). The primary outcome for the meta-analysis was deep venous thrombotic events which were defined as DVT or EHIT Type 2, 3, or 4. Secondary outcomes for the meta-analysis were EHIT Type 2, 3, or 4, DVT and PE. Subgroup analyses were performed for both the RFA and EVLA groups. Pooled proportions were calculated using random effects modelling.

Results: Fifty-two studies (16,398 patients) were included. Thrombotic complications occurred infrequently. Deep venous thrombotic events occurred in 1.7% of cases (95% CI 0.9–2.7%) (25 studies; 10,012 patients; 274 events). EHIT Type 2, 3, or 4 occurred in 1.4% of cases (95% CI 0.8–2.3%) (26 studies; 10,225 patients; 249 events). DVT occurred in 0.3% of cases (95% CI = 0.2%–0.5%) (49 studies; 15,676 patients; 48 events). PE occurred in 0.1% of cases (95% CI = 0.1–0.2%) (29 studies; 8223 patients; 3 events). Similar results were found when the RFA and EVLA groups were analysed separately.

Conclusion: Thrombotic events occur infrequently following GSV EVTA. Given the large numbers of procedures worldwide and the potential for serious consequences, further research is needed on the burden of these complications and their management.

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INTRODUCTION

There has been rapid growth in the use of endovenous thermal ablation of varicose veins. In 2013, the National Institute for Health and Care Excellence (NICE) recommended endovenous thermal ablation (EVTA) as the preferred treatment option for symptomatic varicose veins.[1] This treatment modality causes heat induced vessel wall injury with thrombotic and fibrotic occlusion[2] leading to concerns regarding the potential for venous thromboembolism (VTE).[3] Although the complications of deep venous thrombosis (DVT) and pulmonary embolism (PE) are thought to be rare, the Society for Vascular Surgery recommends that patients undergo early post-procedural

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duplex scanning to detect potential thrombotic events.[2] Notably, the European Society for Vascular Surgery does not make such a recommendation.[4]

The routine use of duplex surveillance has led to the description of a new form of localised post-operative DVT which is termed endovenous heat induced thrombosis (EHIT)[5] and refers to the extension of thrombus from the ablated superficial vein into the deep vein. Four subtypes of EHIT have been described: Type 1, thrombus flush with the junction between superficial and deep vein; Type 2, thrombus extension into the deep vein, cross sectional area $\leq$50%; Type 3, thrombus extension into the deep vein, cross sectional area $>$50%; Type 4, complete occlusion of the deep vein. EHIT is a relatively new entity, little is known about its natural history or potential clinical relevance. In the literature, reported rates of EHIT vary from 0% to 8%[2,6] with no clear consensus on its management.

Given the large numbers of EVTA procedures that take place worldwide, and the potential for severe complications, it is important that healthcare providers appreciate the true rate of VTE complications. Such information may help to guide decision making for individual patients and may streamline research on methods of VTE prevention. For these reasons, a systematic review and meta-analysis of the incidence of VTE complications following great saphenous vein (GSV) EVTA was performed.

METHODS

The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42018089260) and the protocol is available online.[7] Eligible studies were randomised controlled trials or case series which included at least 100 adults who underwent GSV ablation for symptomatic reflux via endovenous laser ablation (EVLA) or radiofrequency ablation (RFA) and had duplex ultrasound (DUS) surveillance scanning within 1 month of the procedure. Both prospective and retrospective studies were included and patients in eligible studies could additionally have concomitant treatment of non-truncal varicosities by phlebectomies or foam sclerotherapy and/or perforator ligation. Studies involving the treatment of GSV truncal reflux with EVLA or RFA combined with other modalities such as open surgical ligation of the saphenofemoral junction (SFJ) or other endovenous modalities were excluded. Similarly, studies that did not report on the incidence of DVT, PE, and EHIT were excluded as were studies that reported on treatment of a variety of superficial venous trunks (such as great saphenous, small saphenous, anterior accessory saphenous) without specifically reporting on patients who had great saphenous ablation in isolation. Eligibility was limited to studies that were reported in English. Regarding the sample size constraint that was imposed, eligibility was restricted to studies with at least 100 patients because VTE is thought to be an uncommon event. This cut off point was chosen arbitrarily; a previous review on the topic chose a minimum sample size of 150 for case series.[8]

MEDLINE was searched using the following search strategy comprising free text words: [(radiofrequency OR endovenous ablation OR laser) AND (great saphenous vein)] OR [endovenous heat induced thrombosis]. Embase was searched using the following search strategy comprising words using the "title, abstract, author keyword" option: [(radiofrequency OR endovenous ablation OR laser) AND (great saphenous vein)] OR [endovenous heat induced thrombosis].The search was first performed on April 5, 2017, and a final search for additional studies was performed on February 25, 2018. Two authors (D.H. and D.P.) screened titles and abstracts for eligibility. Full manuscripts of potentially eligible studies were obtained and examined to finalise eligibility. Uncertainties regarding eligibility were resolved by discussion between D.H. and D.P., and when necessary referral to another author (E.K.). The reference lists of eligible articles were scrutinised for additional eligible studies. Conference proceedings from the annual meetings of the Vascular Society of Great Britain and Ireland (2010—2017) and the Society for Vascular Surgery's Vascular Annual Meetings (2010—2017) were also searched for eligible studies that were published only in abstract form (S.K.). For each eligible study, data on the following aspects were extracted independently (D.H. and D.P.) and entered into an electronic spread sheet: author, publication year, study design, treatment modality, numbers of included patients and limbs, age and gender profile of patients, clinical classification of patients' chronic venous disease (CVD), positioning of the EVTA fibre or catheter tip in relation to the SFJ, use of peri-procedural anticoagulation, timing of the first post-procedural DUS, additional concomitant procedures, incidence of DVT, incidence of EHIT, incidence of PE. There were no predefined definitions for DVT or PE: the definitions provided in manuscripts were used if such definitions were provided. EHIT was defined using the classification system outlined in the Introduction.[5] Disagreements regarding extracted data were resolved by discussion between D.H. and D.P.

Outcomes for the systematic review were DVTs, EHIT of all types, and PE. The primary outcome for the meta-analysis was deep venous thrombotic events which were defined as DVT or EHIT Type 2, 3, or 4. Secondary outcomes for the meta-analysis were EHIT Type 2, 3, or 4, DVT, and PE. Additional subgroup analyses were performed for both the RFA and the EVLA groups.

The Down's and Black Tool was used for assessment of study quality.[9] This consists of a total of 27 questions that assess the quality of reporting and internal and external validity. It yields scores that may vary between 0 and 31, including a score of 0—5 for sample size justification. For the purposes of this review, the checklist was modified by giving 1 point for reporting a sample size calculation and 0 points for omitting this. Therefore, studies included in this review could have had scores ranging from 0 to 27, with higher scores indicating higher quality.

Statistical analyses were performed with StatsDirect version 3 (StatsDirect Ltd, Altrincham, UK).[10] Proportion meta-analyses using random effects modelling were used to

determine pooled proportions for outcomes. In all analyses, patients were used as the unit of analysis rather than limbs. Some patients had bilateral treatment and these patients were treated as patients in the denominators of the analyses rather than two limbs. This is important because outcomes from two limbs in one patient cannot be considered to be independent.[11] Cochran's Q test was used to determine statistical heterogeneity among studies. The likelihood of publication bias was assessed via visual inspection of funnel plots and via Egger tests. The 5% level was chosen for significance for all analyses.

RESULTS

The results of the search are summarised in Fig. 1. Seven hundred and thirty one potentially relevant citations were identified. Five hundred and sixty citations were excluded based on titles and abstracts, and 171 full text manuscripts were retrieved and examined. One hundred and twenty six articles were excluded after examining the full manuscripts. These excluded articles are identified in Supplementary Table 1. Seven extra eligible studies were found by searching reference lists of eligible studies, leaving 52 studies finally eligible for inclusion.

The 52 studies which were analysed (16,398 patients) are summarised in Table 1. The studies comprised five single centre randomised controlled trials, five multicentre randomised controlled trials, one cluster randomised controlled trial, 16 prospective single centre case series, two prospective multicentre case series, and 23 retrospective single centre case series. Forty-eight studies were available in manuscript form and four studies were only available in

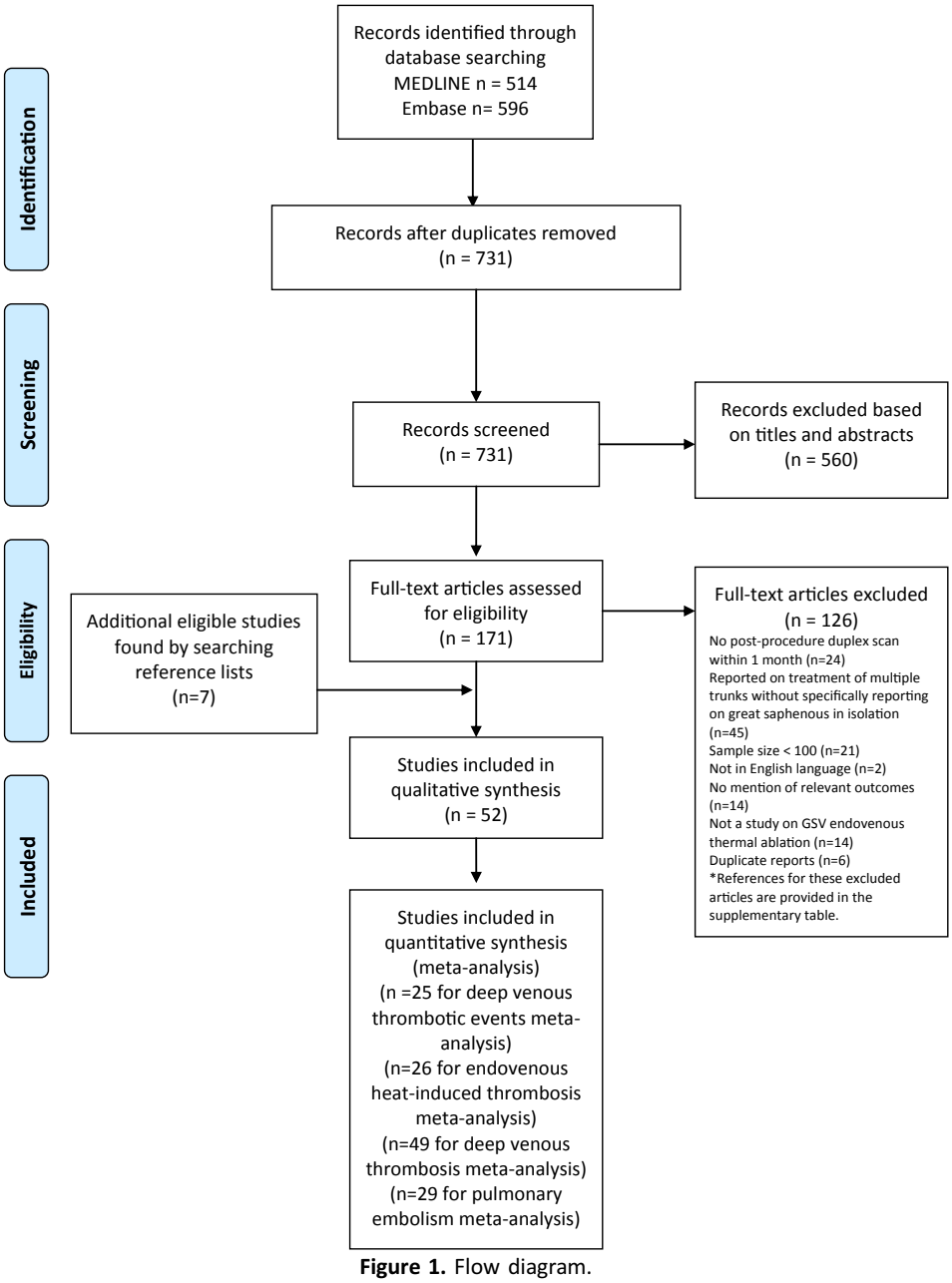

Figure 1. Flow diagram.

Table 1. Characteristics of included studies.

First author	Year	Design	Modality	Number of patients	Number of limbs treated	Male/Female	Details on patients' ages in years	Details on C Class	Placement of fibre or catheter tip	Peri-procedural anticoagulation	Timing of first DUS	Additional concomitant treatments	Quality Score
Weiss[12]	2002	Retrospective single centre CS	ClosurePlus RFA	120	140	38/82	Not reported	Not reported	Not specified	Not specified	1 week	Phlebectomies in 62% of limbs	14
Min[53]	2003	Prospective single centre CS	810-nm laser	423	499	71/352	Mean 42	Not reported	0.5—1 cm distal to SFJ	Not specified	1 week	No concomitant procedures	15
Proebstle[55]	2006	Prospective single centre CS	940-nm laser	203	263	65/138	Median 55-61	Most were C2	1—2 cm distal to SFJ	Dalteparin 2500 IU for 8 days	1 days	No concomitant procedures	18
Welch[60]	2006	Retrospective single centre CS	ClosurePlus RFA	146	184	35/111	Mean 48	Mostly C2	Distal to SEV	Not specified	1 week	7 limbs had concomitant stab phlebectomy	15
Sharif[56]	2006	Prospective single centre CS	810-nm laser	136	145	61/75	Mean 54	Not reported	0.5—1 cm distal to SFJ	Not specified	1 week	Not specified	19
Desmyttere[43]	2007	Prospective single centre CS	980-nm laser	500	511	64/436	Median 53	All were C2	1—2 cm distal to SFJ	Not specified	1 day	Phlebectomies in 98%	14
Jung[45]	2008	Retrospective single centre CS	810-nm laser	112	Not specified	Not reported	Not reported	Mostly C2	2—3 cm distal to SFJ	Not specified	1 week	All had phlebectomies	15
Knipp[6]	2008	Retrospective single centre CS	810-nm laser	364	460	Not reported	Mean 50-51	Half were C2	Either distal to first tributary or 2 cm from SFJ	Selective heparin or enoxaparin use depending upon risk factors	1 month	Phlebectomy or perforator ligation in 30.5% of cases	17
Boros[40]	2008	Retrospective single centre CS	ClosurePlus RFA	142	142	39/103	Mean 53	Not reported	Distal to SEV	Not specified	1 day	Not specified	16
Lugli[50]	2009	Prospective single centre CS	940-nm laser	186	200	52/134	Mean 52	Mostly C2-3	1.5 cm distal to SFJ	Not specified	1 week	No concomitant procedures	20
Puggiono[33]	2009	Retrospective single centre CS	ClosurePlus RFA	274	293	89/185	Mean 60	Mostly C2-4	1 cm distal to SEV	No prophylaxis	5—8 days	Phlebectomies in 30% and perforation ligation in 1%	16
Bhalla[39]	2010	Retrospective single centre CS	Laser (wavelength unspecified)	186	253	120/66	Mean age 45.5 years	Not reported	at SFJ	Not specified	1 week	All had foam sclerotherapy of varicosities and perforators	N/A
Creton[13]	2010	Prospective multi centre CS	ClosureFast RFA	225	295	59/166	Mean 51	Mostly C2 and C3	Distal to SEV	Not specified	3 days	Phlebectomies in 55.6% of cases and sclerotherapy in 12.9% of cases	17
Gale[14]	2010	Single centre RCT	810-nm laser and ClosurePLUS RFA	118	141	33/85	Mean 49	More than half were C1 and C2	Distal to IEV	Not specified	1 week	All had phlebectomies	22

Continued

Table 1-*continued*

First author	Year	Design	Modality	Number of patients	Number of limbs treated	Male/Female	Details on patients' ages in years	Details on C Class	Placement of fibre or catheter tip	Peri-procedural anticoagulation	Timing of first DUS	Additional concomitant treatments	Quality Score
Lawrence[31]	2010	Retrospective single centre CS	Closure RFA and ClosureFast RFA	500	500	120/380	Mean 53	Mostly C2	2—2.5 cm distal to SFJ	Anticoagulation was continued for those already anticoagulated and considered high risk, no prophylaxis was given otherwise	2—3 days	Phlebectomies in an unspecified number of patients	17
Schwarz[21]	2010	Prospective single centre CS	1470-nm laser	286	312	Not reported	Mean 57-61	Mostly C2	Not specified	Enoxaparin 40 mg for 5 days	1 week	Majority had concomitant sclerotherapy of tributaries or below treated vein (numbers unspecified)	17
Vuylsteke[59]	2010	Prospective single centre CS	1500 nm laser	129	158	34/95	Mean 44	Mostly C2-3	Not specified	20 mg enoxaparin for 10 days	1 month	Phlebectomies in all patients	19
Kapoor[15]	2010	Retrospective single centre CS	ClosureFast RFA	100	100	32/68	Mean 42	Mostly C2-3	1—3 cm distal to SFJ	Not specified	2 weeks	No concomitant procedures	16
Khanna[46]	2011	Retrospective single centre CS	Laser (wavelength unspecified)	800	Not reported	Not reported	Not reported	Not reported	3—4 cm below SFJ	Not specified	1 day	Not reported	N/A
Ventoruzzo[57]	2011	Prospective single centre CS	ClosureFAST RFA	225	256	61/164	mean age 54 years	Not reported	Not reported	Not specified	3 days	Not reported	N/A
Carradice[42]	2011	Single centre RCT	600-nm laser	126	126	Not reported	Not reported	Mostly C2	Flush with SFJ	Not specified	1 week	Phlebectomies and perforator ligations in an unspecified number of patients	25
Chaar[30]	2011	Retrospective single centre CS	810-nm laser	564	564	Not reported	Not reported	Not reported	2 cm distal to SFJ	No prophylaxis	2—3 weeks	No concomitant procedures	13
Nordon[54]	2011	Single centre RCT	810-nm laser and ClosureFAST RFA	157	157	Not reported	Mean 46	Most were C2	Not specified	No prophylaxis	1 week	Phlebectomies in all patients	26
Rasmussen[16]	2011	Multicentre RCT	980-nm and 1470-nm laser and VNUS Closure RFA	250	292	72/178	Mean 52	Mostly C2-3	2 cm distal to SFJ	Not specified	3 days	All had phlebectomies	24
Vuylsteke[58]	2011	Multicentre RCT	980-nm and 1500-nm laser	180	180	50/130	Mean 51	Mostly C2-3	1.5 cm distal to SFJ	40 mg enoxaparin for 10 days	1 month	All had phlebectomies	23

Lin[28]	2012	Retrospective single centre CS	1470-nm laser and ClosurePlus/ ClosureFast RFA	245	Not specified	Not reported	Not reported	Not reported	2—3 cm distal to SFJ	Not specified	5—7 days	Phlebectomies in an unspecified number of patients	15
Mao[51]	2012	Retrospective single centre CS	980-nm laser	138	163	65/73	Mean 57	Mostly C2-4	2 cm distal to SFJ	Prophylactic LMWH for 3 days	1 week	Not specified	14
Rass[24]	2012	Multicentre RCT	810-nm laser	185	185	62/124	Mean 48	Mostly C2-3	1—2 cm distal to SFJ	Tinzaparin 42.2 mg for 6 days	1 week	No concomitant procedures	23
Zuniga[61]	2012	Retrospective single centre CS	ClosurePlus and ClosureFast RFA	581	667	Not reported	Not reported	Mostly C3-4	1—2 cm distal to SFJ	Not specified	1 week	Not specified	15
Knittel[47]	2013	Prospective single centre CS	1470 nm laser	173	Not reported	67/106	Mean age 56 years	C2-6	Not reported	Not specified	1 month	Not reported	N/A
Flessenkamper[44]	2013	Multicentre RCT	980-nm laser	142	Not specified	45/97	Mean 48	Mostly C2	2 cm distal to SFJ	Not specified	Day of procedure or 1 day	Phlebectomies in almost all patients although number was not specified	24
Korkmaz[17]	2013	Retrospective single centre CS	ClosureFast RFA	344	Not specified	100/244	Mean 45	Not reported	2—3 cm below SFJ	Not specified	1 month	Phlebectomies in an unspecified number of patients	15
Lurie[27]	2013	Prospective single centre CS	ClosureFast RFA	120	120	45/75	Mean 59	Mostly C1	Not specified	No prophylaxis	36 h	Phlebectomy and sclerotherapy in an unspecified number of patients	16
Sadek[35]	2013	Retrospective single centre CS	810-nm and 1470-nm laser and ClosurePLUS and ClosureFAST RFA	3121	3121	Not reported	Not reported	Mostly C2 and C3	2—2.5 cm distal to SFJ	No prophylaxis	2 days	Phlebectomies in an unspecified number of patients	15
Samuel[22]	2013	Retrospective single centre CS	810-nm laser	224	224	82/142	Median 47-54	Mostly C2	Flush with SFJ	Not specified	1 week	Perforator ligation in an unspecified number of patients and phlebectomies in all patients	17
Spreafico[25]	2013	Prospective single centre CS	980-nm laser	204	204	Not reported	Not reported	Mostly C2	2 cm distal to SFJ	Selective LMWH for those with VTE risk factors	3 days	Phlebectomies in 60.8%	18

Continued

Table 1-*continued*

First author	Year	Design	Modality	Number of patients	Number of limbs treated	Male/Female	Details on patients' ages in years	Details on C Class	Placement of fibre or catheter tip	Peri-procedural anticoagulation	Timing of first DUS	Additional concomitant treatments	Quality Score
Tolva[23]	2013	Retrospective single centre CS	ClosureFast RFA	398	407	Not reported	Mean 55	Not reported	2—3 cm distal to SFJ	4000 IU LMWH for 4 days	7—10 days	Phlebectomies and perforator ligation in an unclear number of patients	16
Spreafico[26]	2014	Prospective single centre CS	1470-nm laser	317	317	108/208	Mean 52	Mostly C2-4	2 cm distal to SFJ	Selective use of LMWH for 6 days in patients with moderate risk of VTE	2 days	Phlebectomies in majority of patients (actual number unclear)	17
Altin[37]	2015	Retrospective single centre CS	1470-nm laser	200	230	118/82	Mean 40	Mostly C2	2 cm distal to SEV	Not specified	1 week	Phlebectomies in 63 patients	13
Kutas[48]	2015	Prospective single centre CS	1470-nm laser	100	100	64/36	Mean 39	Mostly C3	2 cm distal to SEV	Not specified	1 week	All patients had phlebectomies	16
Mese[52]	2015	Single centre RCT	1470-nm laser and CR45i RFA	120	120	Not reported	Not reported	Mean C was 3.4	Not specified	Not specified	1 week	No concomitant procedures	17
Morrison[18]	2015	Multicentre RCT	ClosureFast RFA	114	114	21/93	Mean 51	Mostly C2-3	Not specified	Not specified	1 month	No concomitant procedures	23
Sufian[29]	2015	Cluster RCT	ClosureFast RFA	409	409	84/325	Mean 55	Most were C3 or less	2.5—3 cm distal to SFJ	No prophylaxis	3—5 days	Phlebectomies in 45%	21
Kabnick[36]	2016	Prospective multicentre CS	810 nm, 980 nm, 1470 nm laser	213	213	Not reported	Not reported	Not reported	2—3 cm below SFJ	Not specified	3 days	None	18
Sydnor[19]	2016	Single centre RCT	980-nm laser and ClosureFAST RFA	200	200	43/157	Median age 47-49	Most were C3 or less	1—2 cm distal to SFJ	Not specified	1 week	Sclerotherapy or phlebectomy in 49%	23
Ryer[34]	2016	Retrospective single centre CS	Laser and RFA	842	Not specified	235/607	Mean 51	Most were C3 or less	2—3 cm distal to SFJ	No routine prophylaxis	1 day	Most had phlebectomy	18
Hicks[32]	2016	Retrospective single centre CS	ClosureFast RFA	299	Not specified	106/193	Median 55	Mostly C2	At least 2 cm distal to SFJ	Heparin 5000 mg S/C if deemed high risk	2 days	Phlebectomies in 71%	18
Kim[69]	2017	Prospective single centre CS	ClosureFAST RFA	100	139	41/59	Mean age 58 years	Mostly C2-3	2—2.5 cm below SFJ	Not specified	3 days	112/139 limbs had concomitant phlebectomy and 93 had perforator ligation	17
Koramaz[20]	2017	Retrospective single centre CS	1470-nm laser	189	189	95/94	Mean 47	Half were C3	0.5 cm distal to SEV	Not specified	1 week	Phlebectomies in an unspecified number of patients	14

Arslan[38]	2017	Retrospective single centre CS	980-nm laser and 1470-nm laser	400	419	201/199	Mean 38	Not reported	2 cm distal to SFJ	Not specified	1 day	Most had phlebectomy	16
Cabrero Fernandez[41]	2017	Prospective single centre CS	ClosureFast RFA	257	257	96/161	Mean 50	Mostly C2-3	2 cm distal to SFJ	Enoxaparin 40 mg or bemiparin 3500 IU for 7 days	30 days	All had phlebectomies	19
Lawson[49]	2018	Prospective single centre CS	ClosureFAST RFA and 1470-nm laser	311	346	81/230	Mean age 50 years	Mostly C2-4	1.5–2 cm below SFJ	Single pre-procedural dose of nadroparin 0.3 mL	1 week	Foam sclerotherapy of varicosities after 1 week	17

CS = case series; DUS = duplex ultrasound; IEV = inferior epigastric vein; IU = international units; LMWH = low molecular weight heparin; RCT = randomised controlled trial; RFA = radiofrequency ablation; SEV = superficial epigastric vein; SFJ = saphenofemoral junction.

abstract form. Nine studies involved the use of both laser and RFA, 26 studies involved laser only, and 17 involved RFA only. Regarding study participants, females outnumbered males and the mean age of participants in studies ranged from 38 years to 61 years. Most patients suffered from CVD classified as C2C3 according to the CEAP classification. Placement of the fibre or catheter tip also varied: most studies reported tip placement at points between 0.5 cm and 3 cm distal to the SFJ, some studies reported tip placement just distal to the junction with the superficial epigastric vein, some studies reported tip placement at the SFJ, one study reported tip placement 3–4 cm distal to the SFJ while some studies did not provide details on tip placement. Regarding peri-procedural anticoagulation, nine studies reported its routine use, five studies reported selective use, six studies reported no anticoagulation, one study reported no routine use of anticoagulation, and in 31 studies the use of anticoagulation was not clarified (summarised in Table 1). The timing of the first post-procedural DUS ranged from the day of the procedure to day 30 with 42 studies reporting that the first DUS took place within the first 7 days. Most of the studies reported some additional concomitant treatment of non-truncal varicosities by either phlebectomies, sclerotherapy, or perforator ligation (summarised in Table 1). Quality scores ranged from 13 to 26 (Supplementary Table 2). In all of the studies, lower limb thrombotic events were diagnosed by DUS scanning. Potential PEs were investigated only in cases of clinical concern and no study reported routine post-procedural screening for PE.

Table 2 summarises the outcomes. There were 48 reported cases of DVT among 49 studies (15,676 patients). There were 302 cases of EHIT of varying types among 27 studies (10,325 patients). There were 3 cases of PE among 29 studies (8223 patients).

Twenty five studies (10,012 patients; 274 events) yielded data on both EHIT Types 2–4 and DVTs[6,12–35] and these data were pooled for the meta-analysis on the primary outcome of deep venous thrombotic events (EHIT Types 2–4 and DVT). The pooled proportion was 0.017 (95% CI 0.009 to 0.027) (Fig. 2). There was evidence of statistical heterogeneity (Cochran Q $p < .01$), the funnel plot was asymmetrical and the Egger test also suggested publication bias ($p = .01$).

Twenty-six studies (10,225 patients; 249 events) yielded data on EHIT Types 2, 3, or 4.[6,12–36] The pooled proportion was 0.014 (95% CI 0.008–0.023). There was evidence of statistical heterogeneity (Cochran Q $p < .01$), the funnel plot was asymmetrical and the Egger test also suggested publication bias ($p = .02$).

Forty-nine studies (15,676 patients; 48 events) yielded data on DVTs.[6,12–28,30–35,37–61] The pooled proportion was 0.003 (95% CI 0.002–0.005). There was evidence of statistical heterogeneity (Cochran Q $p < .01$). The funnel plot was asymmetrical and the Egger test suggested publication bias ($p < .01$).

Twenty-nine studies (8223 patients; 3 events) yielded data on PEs.[6,12,13,16,18,21,26,28–30,32–34,37,38,41,42,45–48,50–52,54–57,61]

Table 2. Outcomes.

Author	Year	Number of patients	DVT	EHIT of all types	EHIT Types 2, 3 or 4	EHIT Type 2, 3, 4 and DVT	PE
Weiss[12]	2002	120	0	No thrombus extension to CFV	0	0	0
Min[53]	2003	423	0	Not reported	Not reported	Not reported	Not reported
Proebstle[55]	2006	203	0	Not reported	Not reported	Not reported	0
Welch[60]	2006	146	0	Not reported	Not reported	Not reported	Not reported
Sharif[56]	2006	136	0	Not reported	Not reported	Not reported	0
Desmyttere[43]	2007	500	0	Not reported	Not reported	Not reported	Not reported
Jung[45]	2008	112	0	Not reported	Not reported	Not reported	0
Knipp[6]	2008	364	3	32 cases of thrombus extension to CFV	32	35	1
Boros[40]	2008	142	5	Not reported	Not reported	Not reported	Not reported
Lugli[50]	2009	186	0	Not reported	Not reported	Not reported	0
Puggiono[33]	2009	274	7 cases of calf DVT	24 ″had protrusion of thrombus to SFJ″, 7 cases of CFV thrombus	31	38	0
Bhalla[39]	2010	186	0	Not reported	Not reported	Not reported	Not reported
Creton[13]	2010	225	0	No thrombus extension to CFV	0	0	0
Gale[14]	2010	118	1 peroneal DVT (in a laser patient)	No thrombus extension proximally from SFJ	0	1	Not reported
Lawrence[31]	2010	500	0	21 Type 1 EHIT; 8 Type 2 EHIT; 5 Type 3 EHIT; 0 Type 4 EHIT	13	13	Not reported
Schwarz[21]	2010	286	1	1 case of thrombus extension from GSV to CFV	1	2	1
Vuylsteke[59]	2010	129	0	Not reported	Not reported	Not reported	Not reported
Kapoor[15]	2010	100	0	No thrombus extension to CFV	0	0	Not reported
Khanna[46]	2011	800	0	Not reported	Not reported	Not reported	0
Ventoruzzo[57]	2011	225	0	Not reported	Not reported	Not reported	0
Carradice[42]	2011	126	0	Not reported	Not reported	Not reported	0
Chaar[30]	2011	564	2	8 had thrombus extension into deep veins	8	10	0
Nordon[54]	2011	157	0	Not reported	Not reported	Not reported	0
Rasmussen[16]	2011	250	0	No thrombus extension to CFV	0	0	0
Vuylsteke[58]	2011	180	0	Not reported	Not reported	Not reported	Not reported
Lin[28]	2012	245	0	3 Type 1 EHIT; 5 Type 2 EHIT; 2 Type 3 EHIT	7	7	0
Mao[51]	2012	138	0	Not reported	Not reported	Not reported	0
Rass[24]	2012	185	1 gastrocnemius vein thrombosis	2 cases of thrombus extension to CFV	2	3	Not reported
Zuniga[61]	2012	581	11	Not reported	Not reported	Not reported	0
Knittel[47]	2013	173	0	Not reported	Not reported	Not reported	0
Flessenkamper[44]	2013	142	1 thigh DVT	Not reported	Not reported	Not reported	Not reported
Korkmaz[17]	2013	344	0	No EHIT	0	0	Not reported
Lurie[27]	2013	120	1 posterior tibial vein thrombosis and 1 gastrocnemius vein thrombosis	4 Type 1 EHIT, one case each of Types 2, 3 and 4	3	5	Not reported

Table 2-*continued*

Author	Year	Number of patients	DVT	EHIT of all types	EHIT Types 2, 3 or 4	EHIT Type 2, 3, 4 and DVT	PE
Sadek[35]	2013	3121	0	74 Type 2 EHIT	74	74	Not reported
Samuel[22]	2013	224	0	One case of thrombus extension partially occluding the CFV	1	1	Not reported
Spreafico[25]	2013	204	0	2 Type 2 EHIT	2	2	Not reported
Tolva[23]	2013	398	0	1 Type 2 EHIT	1	1	Not reported
Spreafico[26]	2014	317	0	5 Type 2 EHIT	5	5	0
Altin[37]	2015	200	0	Not reported	Not reported	Not reported	0
Kutas[48]	2015	100	0	Not reported	Not reported	Not reported	0
Mese[52]	2015	120	0	Not reported	Not reported	Not reported	0
Morrison[18]	2015	114	0	No thrombus extension to CFV	0	0	0
Sufian[29]	2015	409	Only EHIT was reported	4 Type 1 EHIT; 3 Type 2 EHIT; 3 Type 3 EHIT; 1 Type 4 EHIT	7	7	0
Kabnick[36]	2016	213	Not reported	0	0	Not reported	Not reported
Sydnor[19]	2016	200	0	0	0	0	Not reported
Ryer[34]	2016	842	3	43 Type 2—4 EHIT (subtypes were unspecified)	43	46	1
Hicks[32]	2017	299	5 isolated calf vein thromboses	16 Type 1 EHIT; 12 Type 2 EHIT; 2 Type 3 EHIT; 5 Type 4 EHIT	19	24	0
Kim[69]	2017	100	Not reported explicitly	2 (subtypes unspecified)	Not reported	Not reported	Not reported
Koramaz[20]	2017	189	0	3 Type 1 EHIT	0	0	Not reported
Arslan[38]	2017	400	4	Not reported	Not reported	Not reported	0
Cabrero Fernandez[41]	2017	257	1	Not reported	Not reported	Not reported	0
Lawson[49]	2018	311	1 crural DVT in the laser group	Not reported	Not reported	Not reported	Not reported

CFV = common femoral vein; DVT = deep vein thrombosis; EHIT = endovenous heat induced thrombosis; GSV = great saphenous vein; PE = pulmonary embolus; SFJ = saphenofemoral junction.

The pooled proportion was 0.001 (95% CI 0.001—0.002). There was no suggestion of statistical heterogeneity (Cochran Q $p > .99$, the funnel plot was symmetrical and the Egger test did not suggest publication bias ($p = .71$).

Similar results were found when the RFA and EVLA groups were analysed separately. Regarding the RFA subgroup, the analyses yielded the following pooled proportions: deep venous thrombotic events 0.014 (95% CI = 0.003—0.032); EHIT Types 2, 3, or 4 0.012 (95% CI 0.003—0.027); DVT 0.005 (95% CI = 0.002 to 0.01); PE 0.001 (95% CI 0.000—0.002). Regarding the EVLA subgroup, the analyses yielded the following pooled proportions: deep venous thrombotic events 0.013 (95% CI 0.004—0.028); EHIT Types 2, 3, or 4 0.01 (95% CI 0.003—0.022); DVT 0.002 (95% CI 0.001—0.004); PE 0.001 (95% CI 0.000—0.003).

DISCUSSION

In this review, data from 52 studies involving 16,398 patients were analysed, and it was found that thrombotic events occurred infrequently. The meta-analyses found that GSV EVTA was complicated by deep venous thrombotic events in 1.7% of cases (25 studies, 10,012 patients, 274 events), by DVT in 0.3% (49 studies, 15,676 patients, 48 events), and by PE in 0.1% (29 studies, 8223 patients, 3 events). Similar results were found when the RFA and EVLA groups were analysed separately. Limb thrombotic events were diagnosed by post-procedural DUS, whereas potential PEs were investigated only in cases of clinical concern. This is the largest systematic review on the topic to date and the results are timely given that CVD is highly prevalent[62] and given that there has been enormous growth in the use of EVTA worldwide. Over 300,000 procedures were performed in the USA in 2012;[63] therefore, patients and care providers must have accurate data on complication rates in order to guide decision making. It is likely that the use of EVTA will continue to increase because it is recommended by evidence based guidelines as the preferred treatment for patients with symptomatic varicose veins.[1,3,4]

A previous systematic review by Dermody et al.[8] involving randomised controlled trials and case series on EVTA and foam sclerotherapy found VTE and EHIT rates of <1%. Notably, randomised controlled trials of any size were included whereas only case series with >150 patients were

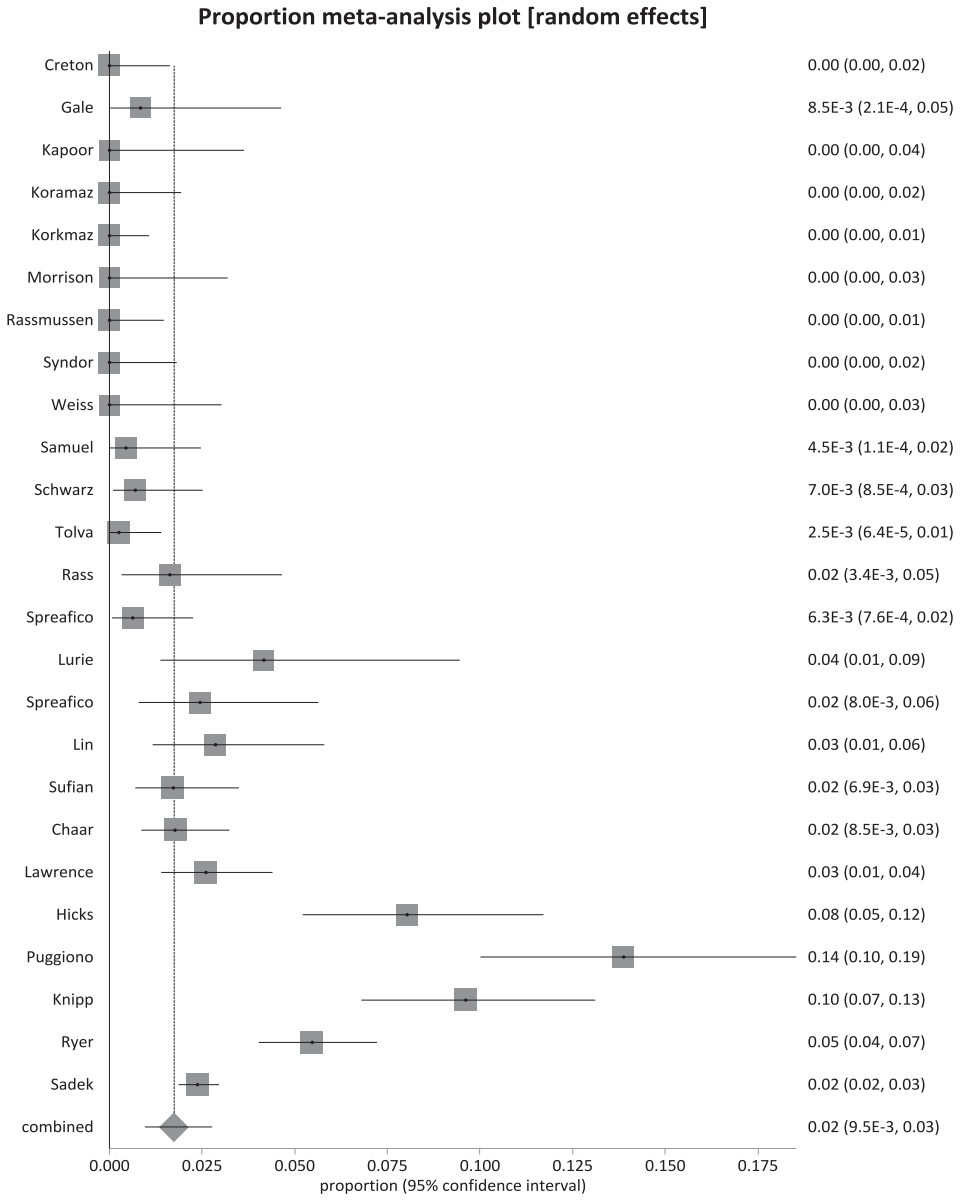

Figure 2. Forest plot for deep venous thrombotic events.

eligible in that review. Limbs were the unit of analysis (rather than patients) and pooled event rates were determined for DVT, PE, and EHIT in each therapeutic group. In contrast, studies with $\geq$100 patients were included in the review, studies that used the older generation ClosurePLUS RFA device were not excluded, and patients were used as the unit of analysis. In spite of these methodological differences, the finding of a 1.7% pooled incidence rate for the primary outcome is broadly similar to the results generated by Dermody et al. and this enhances the validity of both reviews. Another review by Dermody et al.[64] that included randomised controlled trials only found pooled incidence rates for VTE to be 0.5% and 0.4% for ClosureFAST RFA and laser ablation respectively. However, it is possible that event rates are higher in everyday clinical practice: O'Donnell et al.[63] used a large scale retrospective registry to evaluate rates of DVT and PE within 30 days of surgery, endovenous ablation or sclerotherapy for varicose veins. Surprisingly, RFA was complicated by DVT and PE in 4.4% and 0.3% of cases respectively and the corresponding results for laser ablation were 3.1% and 0.3%. There were no reported fatal VTE complications in the current review but in the real life report by O'Donnell et al. there were 19 deaths within 30 days of EVTA in 44,617 patients that may have resulted from VTE complications. The cause of the discrepancy between the results of the current review and the real life results of O'Donnell et al. is unknown. Publication bias is a possibility: individuals with higher complication rates may have been less likely to publish their results or partake in trials. Notably, statistical evidence for publication bias was found in the meta-analyses of deep venous thrombotic events, EHIT Type 2, 3, and 4, and DVT. Technical variability in procedures may not adequately explain the discrepancy nor can patients' comorbidities because mean comorbidity scores were low in the O'Donnell et al. study. It was noted that a limitation of the O'Donnell study was that individual

cases of thromboembolism associated with a recent intervention were not examined to verify the accuracy of coding in terms of clinical information. Additionally it is our anecdotal experience that a post-operative duplex scan in a symptomatic patient that demonstrates GSV thrombus may be incorrectly reported as a post-operative complication by an operator that is unfamiliar with the intervention performed. Nevertheless the O'Donnell paper raises the possibility of a higher thromboembolic complication rate in "real world" practice and cannot be dismissed lightly. Further real life registry based studies are urgently needed.

Although the endovenous revolution is firmly established, there are many unanswered questions and there is a need for further research. Little is known about the natural history of EHIT and there is no firm evidence to guide its treatment. Considerable variation in approaches to EHIT treatment were noted. Lawrence et al.[31] proposed that Type 1 EHIT may be treated on a case by case basis with either observation or anticoagulation and recommended anticoagulation for the other EHIT subtypes. They noted no case of thrombus progression among patients with Type 1 EHIT that were managed with observation or anticoagulation. Sadek et al.,[35] Hicks et al.,[32] and Jones et al.[65] proposed observation for Type 1 EHIT and anticoagulation for the other subtypes with early discontinuation of anticoagulation for those with Type 2 EHIT with DUS confirmed thrombus regression. Knipp et al.[6] treated patients with thrombus extension with 1 week of anticoagulation and a repeat DUS and they described that in almost all cases, the thrombus regressed so that no further treatment was required. Puggioni et al.[33] suggested the use of antiplatelet therapy with serial DUS until resolution and they reserved anticoagulation for those with thrombus progression on surveillance imaging. Ryer et al.[34] highlighted that EHIT progression occurred in 13% of patients with Type 1 EHIT managed with just observation, and consequently they proposed anticoagulation for every case of EHIT. These suggestions for the management of EHIT were based upon small sample sizes and no convincing evidence based treatment strategy exists. Furthermore, potential complications from anticoagulation cannot be underestimated.

Regarding the prediction of EHIT, some potential risk factors may have emerged but these require further research: concomitant phlebectomy,[32] prior VTE,[31,32] prior superficial thrombophlebitis,[33] larger GSV diameter,[31,33,66] higher CEAP clinical class,[66] and elevated d-dimer with normal C reactive protein[27] have been proposed to be associated with EHIT.

Considerable variation regarding the use of peri-procedural anticoagulation among the studies included in this review was found (Table 1). In our clinical practice, patients are routinely given a single peri-procedural dose of enoxaparin 20 mg (or 40 mg if clinically indicated), accepting that this practice is not supported by evidence. A recent survey of Irish vascular surgeons indicated that most adopt a similar practice.[67] It is interesting to note that most of the studies in the review either did not comment on peri-procedural anticoagulation or else reported not using peri-procedural anticoagulation. It is worth noting that European and North American guidelines advise selective use of thromboprophylaxis for patients considered to be at increased VTE risk while highlighting the importance of other measures such as early ambulation and a preference for day case procedures for VTE prevention.[3,4]

Considerable variation regarding the timing of post-procedural DUS was noted (Table 1). This may be of considerable significance: Ryer et al.[34] noted that 20 out of 842 patients were diagnosed with EHIT on DUS on the first post-procedural day and that an additional 19 cases of EHIT were diagnosed via DUS a week later. Forty-two of the included studies in this review reported that the first post-procedural DUS took place within 1 week; — it is likely that studies with later use of DUS may have missed cases of early EHIT. The optimal timing of post-procedural DUS for the most efficient and accurate detection of EHIT remains unclear but may become apparent as understanding of the natural history of EHIT improves. The Society for Vascular Surgery gives a Grade 2c recommendation for routine early post-procedural DUS at 24—72 h for the detection of thrombotic events. However, this is difficult to justify in clinical practice because of resource limitations and because it has been demonstrated that thrombotic events are infrequent. Furthermore, given that the sensitivity and specificity of DUS for the detection of DVT are approximately 95%,[68] testing for an event that occurs infrequently will result in an excessive number of false positives with ensuing unnecessary anticoagulation. Notwithstanding this, routine protocolised, post-procedural DUS is absolutely necessary to generate new information in the context of research and therefore has relevance.

The strengths of this review relate to the thorough search strategy, which included a detailed grey literature search, and the large number of studies and patients included. Furthermore, the study quality assessment has added transparency to the review. The principal limitation is that there is a large amount of clinical heterogeneity among the studies. Notwithstanding this, the results are similar to other studies that evaluated the question at hand via different methodology. A large number of studies were excluded, some of which had impressively large sample sizes, because they reported simultaneously on the treatment of a variety of venous trunks without specifically reporting on the subset of patients who had GSV ablation in isolation. These limitations emphasise the need for improved quality of reporting in future studies of endovenous ablation and creating formalised reporting standards would greatly improve comparability among future studies. In particular, future studies should report outcomes by patient and not by limb and should explicitly report protocols for post-procedural DUS. Clinical characteristics of patients may continue to be reported by limb.

CONCLUSION

EVTA of the GSV is infrequently complicated by thrombotic events. Nonetheless, enormous numbers of patients

worldwide undergo EVTA and it is possible that thrombotic complications, including EHIT, cause a significant clinical burden. There is a need for prospective registries in order to quantify and qualify this burden and further inform the management of these thrombotic complications.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvs.2018.05.008.

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CONFLICT OF INTEREST

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