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Treatments to prevent primary venous ulceration after deep venous thrombosis

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ABSTRACT

Objective: This systematic review and meta-analysis aimed to assess whether compression stockings or other interventions reduce the incidence of venous ulceration after acute deep venous thrombosis.

Methods: We searched PubMed and Embase for randomized controlled trials (RCTs), restricted to English, Spanish, and Hebrew, related to post-thrombotic syndrome and venous ulceration in participants with confirmed deep venous thrombosis. Our primary statistical assessment was the Peto odds ratio (OR).

Results: Our search generated 23 RCTs meeting inclusion and exclusion criteria, summing 6162 patients and 146 ulcerative events. Trials were categorized into compression, low-molecular-weight heparin (LMWH), procedural thrombolysis, medical thrombolysis, or miscellaneous. Six compression trials were identified, of which five were included in meta-analysis. Compression compared with placebo did not reduce venous ulceration (OR, 0.915; 95% confidence interval [CI], 0.475-1.765), and long-term compression was not superior to short-term compression (OR, 1.36; 95% CI, 0.014-1.31). Four LMWH trials were identified but were not subjected to meta-analysis because of intertrial heterogeneity. One trial, comparing extended tinzaparin with warfarin, demonstrated eight ulcers in the warfarin group and one ulcer in the LMWH group (relative risk, 0.125; $P < .05$). Three procedural thrombolysis trials were pooled into meta-analysis; fewer ulcerative events occurred in procedural thrombolysis patients, but the effect was not significant (OR, 0.677; 95% CI, 0.338-1.358). Eight medical thrombolysis trials were identified. Pooled analysis of five trials demonstrated a protective effect on ulceration in streptokinase patients vs standard heparinization (OR, 0.125; 95% CI, 0.021-0.739). However, these trials were of poor-quality study design, had small sample size, and had poor overall outcomes. Miscellaneous studies included a trial of hidrosmina, a vasoactive flavonoid, and a trial comparing 6-month warfarin treatment with 6 weeks; neither trial had significant outcomes. Intertrial heterogeneity was not adequately assessed with the I^2 value as venous ulceration is a rare event; the Grading of Recommendations Assessment, Development, and Evaluation evidence for most trials was very low, with the exception of procedural thrombolysis trials, for which it was low.

Conclusions: We found insufficient evidence to assess whether compression or other interventions protect against venous ulceration. To develop guidelines for treatment decisions related to prevention of venous ulceration, high-powered RCTs investigating venous leg ulcers as a primary outcome are required. (J Vasc Surg: Venous and Lym Dis 2019;7:260-71.)

Keywords: Venous thrombosis; Venous insufficiency; Post-thrombotic syndrome; Venous ulceration, prevention

Chronic venous insufficiency or chronic venous disease (CVD) has a tremendous impact on the national economy and on the quality of life of patients. The most costly and debilitating feature of CVD is venous ulceration, as ulcers generally heal slowly and have high recurrence rates.[1] Venous leg ulcers (VLUs) have a mean total cost upward of $15,000/ulcer. Considering an estimated 1% to 2% prevalence of VLU in the adult population, which is aging, these ulcers represent a massive and rapidly growing burden in health care cost.[2,3] In addition, VLUs cause a significant number of missed workdays, and some estimates have them accounting for 1% of total health care costs.[4,5] Whereas the healing and management of venous ulcers have been studied extensively, there is a paucity of data regarding preventive strategies and especially primary prevention.

CVD is a progressive disease caused by venous reflux, obstruction, or both,[6,7] which leads to sustained, increased ambulatory venous pressures (ie, venous hypertension).[2] Venous hypertension generates fluid transudation and chronic inflammation, resulting in signs and symptoms of CVD.[8] Mild classes of CVD (C1-C3) include telangiectasias, varicose veins, and edema; the more severe classes (C4-C6) include pigmentation, eczematous changes, lipodermatosclerosis, and venous ulcers.[9] Most clinicians recognize the Society for Vascular Surgery and American Venous Forum guidelines for the classification of CVD, known as the Clinical,

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Etiology, Anatomy, and Pathophysiology (CEAP) classification system.[9] Although the pathologic sequence of events giving rise to CVD and leading to CVD progression has not been entirely elucidated, it is generally accepted that identification of early stages of disease confers the opportunity for preventive treatments.[10]

A principal clinical goal in managing CVD is the reduction of modifiable risk factors.[11] Recognized risk factors for CVD incidence include obesity, orthostatism, pregnancy, older age, female sex, and family history of venous disease.[12] The single greatest risk factor for venous ulceration, however, is a history of deep venous thrombosis (DVT).[13] The post-thrombotic syndrome (PTS) is a clinical entity referring to a spectrum of CVD manifestations occurring after acute DVT, ranging from leg swelling and skin changes to venous ulceration. Standard of care in the post-thrombotic period is to encourage the use of compression stockings to curtail PTS; however, evidence that compression prevents PTS is weak, and evidence that compression prevents primary venous ulceration has not been established.[14]

We therefore designed a systematic review and meta-analysis of randomized controlled trials (RCTs), aiming to determine whether compression therapy prevents primary venous ulceration in the post-thrombotic period and to assess whether any other types of interventions in the post-thrombotic period, ranging from selection of anticoagulation to endovascular interventions, prevent primary venous ulceration.

METHODS

Search strategy. In collaboration with a research librarian, we systematically searched MEDLINE and Embase, with language restricted to English, Spanish, and Hebrew, for RCTs in humans related to venous insufficiency or PTS. Our core search consisted of terms related to venous insufficiency or complications thereof (eg, "venous reflux," "leg edema," "varicose vein," "venous ulceration," "stasis dermatitis") and terms specific to PTS (eg, "venous thrombosis," "post-thrombotic syndrome"). For full search strategies, see the Appendix (online only). Using a citation manager, we compiled all results from our search and removed duplicates.

Two reviewers (B.D. and J.J.) independently assessed the resulting studies by title, removing any studies that were grossly unrelated to DVT treatment. Subsequently, the reviewers screened the abstracts of the remaining studies, excluding any articles unrelated to PTS or venous ulceration. Discordance between the reviewers was resolved by discussion or settled by a third-party reviewer (H.L.T.). Any study with insufficient information to be excluded by abstract was included in full-text analysis. Full texts were obtained for all texts passing the abstract screening. Eligibility for data extraction was assessed independently by the two reviewers. Inclusion criteria consisted of DVT documented by ultrasound, RCT comparing intervention with control, documentation of venous ulceration, and documentation of anticoagulation treatment after DVT. Exclusion criteria consisted of ulcers present at baseline and start of trial remote from treatment of DVT (>6 months).

Data extraction. A standardized table for extraction was created that included the following details:

1. Trial methods and categorical study design (treatment vs placebo, treatment vs standard of care, dose response);
2. Durations of treatment dose, characteristics of treatment, duration of follow-up, and presence or absence of compression in treatment for those trials in which compression was not the primary intervention;
3. Patients' baseline characteristics, including sample size, age, sex, and body mass index broken down by study arm; and
4. Total ulcerations broken down by study arm.

Extractions were performed by two reviewers and cross-referenced for accuracy. Patients' data were selected by intention-to-treat analysis. CEAP classifications C5 and C6, for which venous ulceration is inherent in the definition, were accepted as a valid substitution for listing outright venous ulcer data. In the case of studies that alluded to venous ulceration but did not list data, the primary author of the study was contacted by e-mail. Those who responded with data were included in analysis.

Data analysis. Our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15] Studies were categorized into one of five groupings based on primary intervention: compression trials; low-molecular-weight heparin (LMWH) trials; procedural thrombolysis trials; medical thrombolysis trials; and miscellaneous trials. The decision to subject a trial category to meta-analysis was reached qualitatively by the reviewers. The criteria for meta-analysis were based on pooled sample size, subjective determinations of study heterogeneity (discrepancies in treatment dose, treatment time, and length of follow-up), adherence to DVT standard of care guidelines, and presence of confounding variables (ie, some trials included compression as a recommended adjunct to treatment, whereas others did not). In consideration that venous ulceration is typically a rare event (<1%), we used the Peto one-step odds ratio (OR) as the measure of association, given its superiority in meta-analysis of pooled rare events where ORs are close to 1.[16] Trials in which zero ulcers were reported in either arm were excluded from meta-analysis as they are incompatible with Peto OR. Evaluation of heterogeneity was determined by the Cochrane I^2 value. However, we caution that statistical assessments of heterogeneity are significantly less valuable in the context of rare events[17] like venous ulceration. Quality of the evidence was evaluated by the Cochrane

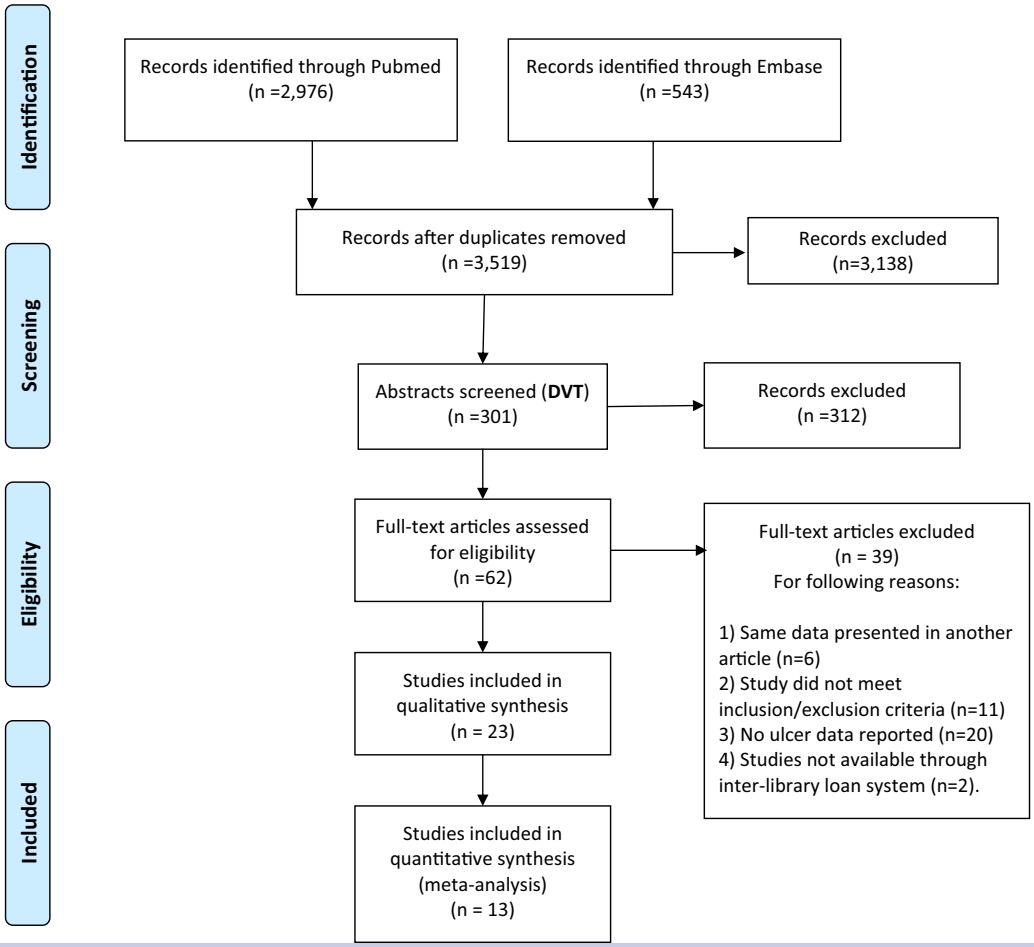

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for search selection strategy. *DVT,* Deep venous thrombosis.

Table I. Summary of study characteristics for compression trials

Study author	Study arm											No. of patients	Follow-up, months	Ulcers, No. (%)	Meta-analysis
Aschwanden[22]	Arm 1	C, H, W	C, W	C, W	C, W	C, W	C	C	C			84	38	0	No
	Arm 2	P, H, W	P, W	P, W	P, W	P, W	P	P	P			85	33	0	No
Brandjes[23]	Arm 1	C, H, W	C, W	C, W	C, W	C, W	C	C	C	C	C	96	76	1 (1)	Yes
	Arm 2	P, H, W	P, W	P, W	P, W	P, W	P	P	P	P	P	98	76	3 (3)	Yes
ten Cate-Hoek[24,a]	Arm 1	AC, C	AC, C	AC, C	AC, C	AC, C	AC, I	AC, I				437	24	2 (0.5)	Yes
	Arm 2	AC, C	AC, C	AC, C	AC, C	AC, C	AC, C	AC, C				428	24	0	Yes
Kahn[25,b]	Arm 1	C, H, W	C, W	C, W	C, W	C, W	C	C				409	24	17 (4.2)	Yes
	Arm 2	P, H, W	P, W	P, W	P, W	P, W	P	P				394	24	16 (4.1)	Yes
Mol[26,b]	Arm 1	C, H, W	C, W	C, W	C, W	C, W	C	C				262	24	0	Yes
	Arm 2	C, H, W	C, W	C, W	C, W	C, W	C					256	24	1 (0.4)	Yes
Roumen-Klappe[27]	Arm 1	C, H, W	C, W	C, W	C, W	C	C					31	12	0	No
	Arm 2	C, H, W	C, W	C, W	C, W	C	C					33	12	0	No
Months since randomization		0	1	2	3	6	12	24	36	48	72				

AC, Mixed anticoagulation; *C,* compression stockings; *H,* heparin; *I,* individualized compression; *P,* placebo stockings; *W,* warfarin.
[a]Anticoagulation varied by local site protocol. Most patients received heparinization to warfarin, but some patients received extended heparins or novel anticoagulants.
[b]Anticoagulation was not performed by study investigators, but most patients were documented to have received standard of care, such that studies were deemed appropriate for meta-analysis.

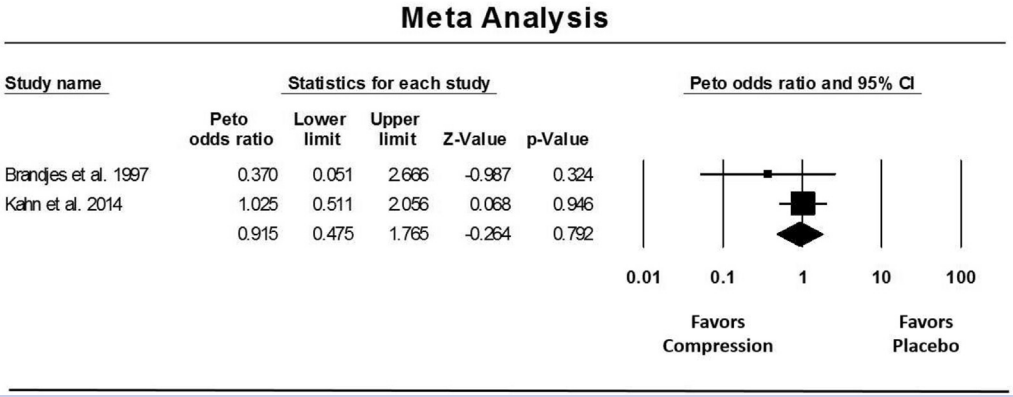

Fig 2. Peto odds ratio (OR) with 95% confidence interval (*CI*) for the development of venous leg ulcers (VLUs) in trials comparing compression stockings with placebo. Meta-analysis of trials is listed in the third row.

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria using the Cochrane GRADEpro software (McMaster University, 2015; developed by Evidence Prime, Inc). Statistical analysis was performed by StatsDirect version 3.1.14 (StatsDirect Ltd, Cambridge, United Kingdom) and Comprehensive Meta-Analysis version 3.3.070 (Biostat, Englewood Cliffs, NJ) software.

RESULTS

Fig 1 shows our selection process in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[15] After duplicates were removed, a total of 3519 citations were generated by our search strategy, which was run initially on October 27, 2016, and then updated on February 1, 2018. Following the screening of titles and abstracts, 62 articles were included in full-text analysis, of which two articles could not be retrieved even by our interlibrary loan system. Independent articles reporting data from the same trials were removed. Four primary authors were contacted for ulcer data not presented in their trial; one did not reply,[18] one did not track ulcer data,[19] and two supplied ulcer data.[20,21] A total of 23 studies were included in data analysis, reflecting data of 6162 patients. All included studies were written in English. Sixteen studies were based in Europe, six in North America (primarily Canada), and one in South Africa. Of these studies, 17 reported non-0 values for ulcer incidence, summing a total of 146 ulcers reported across all studies. In none of the trials was venous ulceration documented as a primary outcome; rather, it was documented as a secondary outcome or adverse event. In addition, no trials presented effect size of interventions on VLU rate or any other statistical measurement regarding VLUs. Six studies were grouped to compression trials, four to LMWH trials, three to procedural thrombolysis, eight to medical thrombolysis, and two to miscellaneous.

Study characteristics of all compression trials with a temporal illustration of treatment plans are illustrated in Table I. Of 6 trials, 3 studies[22,23,25] compared compression stockings with placebo, 1 trial[26] compared compression treatment of 2 years vs 1 year, 1 trial[27] compared compression acutely at time of DVT with no acute compression

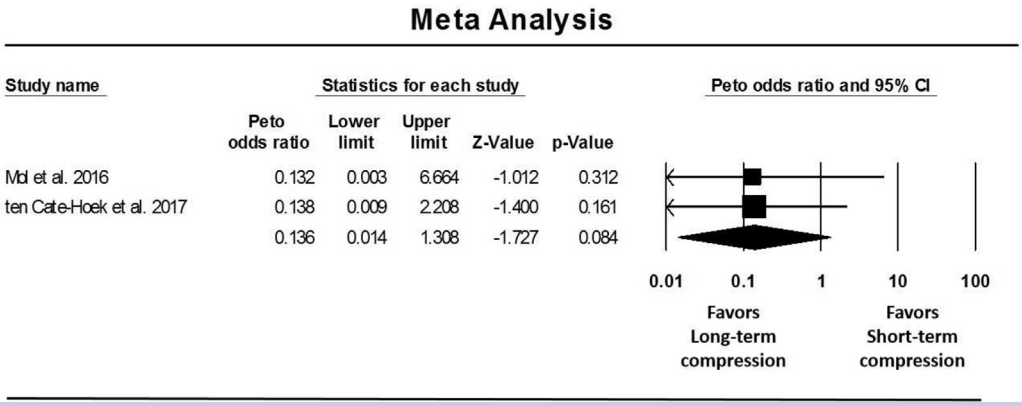

Fig 3. Peto odds ratio (OR) with 95% confidence interval (*CI*) for the development of venous leg ulcers (VLUs) in trials comparing long-term compression stockings (>12 months) with short-term compression stockings (<12 months). Meta-analysis of trials is listed in the third row.

Table II. Summary of study characteristics for low-molecular-weight heparin (LMWH) trials

Study author	Study arm									No. of patients	Follow-up, months	Ulcers, No. (%)
Gonzalez-Fajardo[28]	Arm 1	C, LH	C, LH	C, LH	C, LH	C	C	C	C	56	60	9 (16)
	Arm 2	C, W	C, W	C, W	C, W	C	C	C	C	44	60	7 (16)
Hull[29]	Arm 1	LH	LH	LH	LH					240	12	1 (0.4)
	Arm 2	LH, W	W	W	W					240	12	8 (3.3)
Prandoni[30]	Arm 1	LH								45	12	0
	Arm 2	H								45	12	0
Righini[21]	Arm 1	LH, C	LH, C	C	C					111	3	0
	Arm 2	P, C	P, C	C	C					124	3	0
Months since randomization		0	1	2	3	6	12	18	24			

C, Compression stockings; *H,* heparin; *LH,* low-molecular-weight heparin; *P,* placebo; *W,* warfarin.

treatment, and 1 trial[24] compared 24 months of compression vs individualized length of compression (6-24 months) based on severity of PTS symptoms. Length of treatment ranged from 1 year to 6 years, and average length of follow-up ranged from 12 months to 76 months. Compliance with compression varied between trials but was reported to be similar between arms in all trials. In all trials, the majority of patients were treated with standard of care anticoagulation including immediate heparinization to a warfarin bridge (international normalized ratio of 2-3), with warfarin treatment lasting 3 to 6 months. In the Kahn[25] and Mol[26] studies, anticoagulation was documented but not administered by the investigators. In the ten Cate-Hoek[24] and Kahn[25] trials, anticoagulation varied by study site, and although most patients received the standard anticoagulation protocol (heparin bridge to warfarin), a minority of patients were taking extended heparinization or novel anticoagulants. Compression dose was similar among trials, ranging from 20 mm Hg to 40 mm Hg, all of which were gradient pressure stockings.

Four of the six studies were included in meta-analysis. Compression trials were divided into two separate analyses: two trials comparing compression with placebo[23,25] and two trials comparing longer duration of compression with shorter duration of compression.[24,26] In the ten Cate-Hoek trial, the individualized compression group was treated as the shorter arm of compression, and although some participants in this arm received extended compression (>1 year), the majority (66%) received <12 months of compression vs a standard of 24 months in the other arm. As the Roumen-Klappe study investigated compression acutely at time of DVT (7-14 days) vs no acute treatment, it was held from meta-analysis as its design was different from other trials. The Aschwanden trial reported no ulcers in either arm and was excluded from analysis.

Forest plot illustration of pooled OR analysis for compression vs placebo trials is shown in Fig 2. The OR for the development of venous ulceration in compression groups vs placebo was 0.915 (95% confidence interval [CI], 0.475-1.765). Fig 3 illustrates the forest plot comparing long-term compression with short-term compression. In long-duration compression vs shorter duration, the OR for venous ulceration was 0.136 (95% CI, 0.014-1.308). Statistical heterogeneity in both analyses was low ($I^2 = 0$).

Table III. Summary of study characteristics for procedural thrombolysis trials

Study author	Study arm								No. of patients	Follow-up, months	Ulcers, No. (%)	Meta-analysis
Enden[31,a]	Arm 1	PT, LH, W, C	W, C	W, C	W, C	W, C	C	C	101	24	0	No
	Arm 2	LH, W, C	W, C	W, C	W, C	W, C	C	C	108	24	0	No
Sharifi[32,a]	Arm 1	PT, LH, W, C, A	W, C, A	W, C, A	W, C, A	W, C, A			91	30	1 (1.1)	Yes
	Arm 2	LH, W, C	W, C	W, C	W, C	W, C			92	30	3 (3.2)	Yes
Vendantham[33,b]	Arm 1	PT, AC, C	AC, C	AC, C	AC, C	AC, C	AC, C	AC, C	336	24	12 (3.6)	Yes
	Arm 2	AC, C	AC, C	AC, C	AC, C	AC, C	AC, C	AC, C	355	24	17 (4.8)	Yes
Months since randomization		0	1	2	3	6	12	24				

A, Aspirin; *AC,* mixed anticoagulation; *C,* compression stockings; *LH,* low-molecular-weight heparin; *PT,* procedural thrombolysis; *W,* warfarin.
[a]Length of warfarin treatment is inferred on the basis of standard of care because it is not listed in the trial.
[b]Anticoagulation was documented but not administered by the investigators; anticoagulation included heparins, LMWH, rivaroxaban, warfarin, other anticoagulant, and antiplatelet therapy, in any combination.

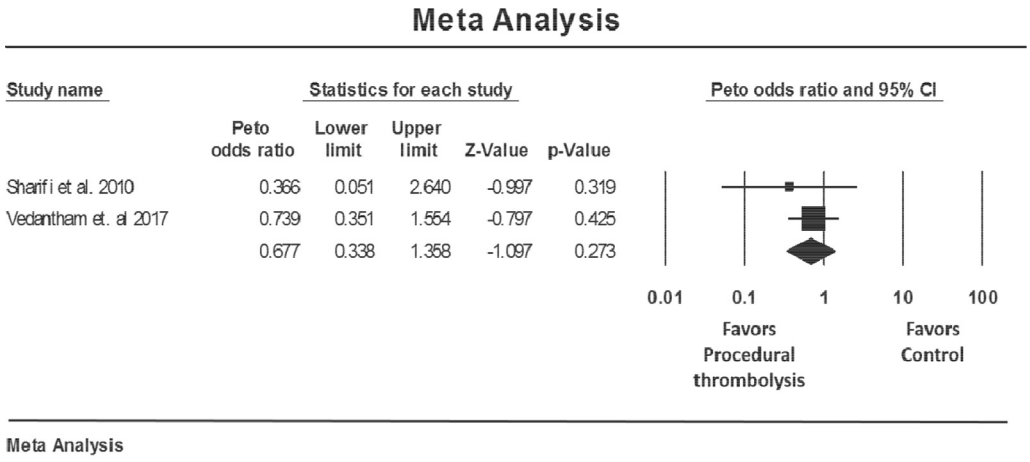

Fig 4. Peto odds ratio (OR) with 95% confidence interval (*CI*) for the development of venous leg ulcers (VLUs) in trials comparing procedural thrombolysis with medical therapy. Meta-analysis of trials is listed in the third row.

The study characteristics of trials involving LMWHs after acute DVT are illustrated in Table II. Two studies compared extended LMWHs with heparin with warfarin bridge,[28,29] an older trial compared LMWH alone with heparin alone,[30] and one trial compared LMWH with placebo injections for DVTs confined to the calf.[21] Warfarin use extended to 3 months in both trials. The Gonzalez-Fajardo trial instructed patients in both arms to wear compression stockings (40 mm Hg) for 2 years, but compliance rates were not reported. The type of LMWH

Table IV. Summary of study characteristics for medical thrombolysis trials

Study author	Study arm							No. of patients	Follow-up, months	Ulcers, No. (%)	Meta-analysis
Arnesen[35]	Arm 1	SK						17	76	0	Yes
	Arm 2	H						18	77	3 (16.7)	Yes
Bieger[36]	Arm 1	SK, H, W	W	W	W	W		5	6	0	No
	Arm 2	H, W	W	W	W	W		5	6	0	No
	Arm 3	W	W	W	W	W		5	6	0	No
Common[37,a]	Arm 1	SK, W	W	W	W	W		15	7	0	Yes
	Arm 2	H, W	W	W	W	W		12	7	1 (8.3)	Yes
Elliot[38]	Arm 1	SK, W	W	W				26	12	0	Yes
	Arm 2	H, W	W	W				26	12	1 (3.8)	Yes
Schulman[39]	Arm 1	SK-hd, H, W	W	W	W	W		39	24	1 (2.5)	No
	Arm 2	SK-ld, H, W	W	W	W	W		41	24	1 (2.4)	No
Schulman[40]	Arm 1	SK, H, W	W	W	W	W		17	24	0	No
	Arm 2	H, W	W	W	W	W		19	24	0	No
Schweizer[41,a]	Arm 1	TPA, H, W, C	W, C	W, C	W, C	W, C	C	23	12	2 (8.7)	No
	Arm 2	UK, H, W, C	W, C	W, C	W, C	W, C	C	23	12	1 (4.3)	No
	Arm 3	H, W, C	W, C	W, C	W, C	W, C	C	23	12	1 (4.3)	No
Schweizer[42]	Arm 1	TPA, H, W, C	W, C	W, C	W, C	W, C	W, C	50	12	1 (2)	No
	Arm 2	UK-hd, H, W, C	W, C	W, C	W, C	W, C	W, C	50	12	2 (4)	No
	Arm 3	UK-ld, H, W, C	W, C	W, C	W, C	W, C	W, C	50	12	3 (6)	No
	Arm 4	SK, H, W, C	W, C	W, C	W, C	W, C	W, C	50	12	0	No
	Arm 5	H, W, C	W, C	W, C	W, C	W, C	W, C	50	12	0	No
Months since randomization		0	1	2	3	6	12				

C, Compression stockings; *H*, heparin; *SK*, streptokinase; *SK-hd*, streptokinase high dose; *SK-ld*, streptokinase low dose; *TPA*, recombinant tissue plasminogen activator; *UK*, urokinase; *UK-hd*, urokinase high dose; *UK-ld*, urokinase low dose; *W*, warfarin.
[a]Length of warfarin treatment is inferred on the basis of standard of practice.

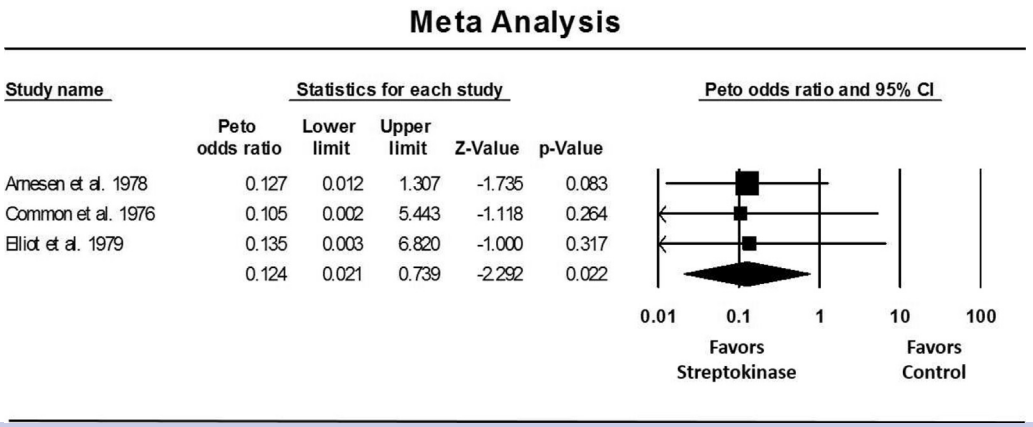

Fig 5. Peto odds ratio (OR) with 95% confidence interval (*CI*) for the development of venous leg ulcers (VLUs) in trials comparing thrombolytics with heparin therapy. Meta-analysis of trials is listed in the fourth row.

varied between trials: one used enoxaparin,[28] one tinzaparin,[29] one Fraxiparine (CY216),[30] and one nadroparin.[21] Mean follow-up times ranged from 3 months to 5 years. Two studies reported non-0 values for ulcers. In the Gonzalez-Fajardo study, ulcer rates were similar between the LMWH arm (0.16) and the heparin arm (0.159); in the Hull study, ulcer rates in the LMWH arm were significantly lower than in the heparin arm (relative risk, 0.125; $P < .05$). Given the marked difference in length of follow-up, study design, use of compression, and treatment protocols, LMWH trials were not subjected to meta-analysis.

The three trials meeting criteria for procedural thrombolysis are listed in Table III. In all trials, a catheter-directed thrombolysis with variable use of angioplasty and stenting was compared against standard of care. The Enden[31] and Sharifi[32] trials both used LMWH (enoxaparin or dalteparin) into a warfarin bridge. Warfarin length of treatment was not listed in either trial but was assumed to be 3 to 6 months on the basis of standard of care guidelines.[34] In the Vedantham trial,[33] anticoagulation was site specific; patients received long-term heparin therapy, warfarin, rivaroxaban, or other anticoagulants according to standard guidelines. Compression was used in all trials: 2 years in the Enden and Vedantham trials and 6 months in the Sharifi trial. Compliance with compression was reported in the Enden trial (78% for procedural thrombolysis arm and 68% for standard of care) and Vedantham trial (55% for both arms at 24 months) but not in the Sharifi trial. Patients in the procedural arm of the Sharifi trial were also instructed to take aspirin 81 mg or clopidogrel if they had a stent placed. Antiplatelet therapy was documented in the Vedantham trial but was not listed as protocol. Length of follow-up was similar between trials (24-30 months). Non-0 values for ulcers were reported in the Sharifi and Vedantham trials. No ulcers occurred in the Enden trial, and it was held from meta-analysis.

Pooled analysis of procedural thrombolysis trials generated 854 participants and 33 total ulcers. Peto OR for the development of venous ulceration in procedural thrombolysis participants vs standard of care, listed in Fig 4, was 0.677 (95% CI, 0.338-1.358).

Eight trials, listed in Table IV, met criteria for medical thrombolysis; the experimental thrombolytics included streptokinase, urokinase, and recombinant tissue plasminogen activator. All of the trials were conducted in or before 2000 and were of modest sample size (maximum of 50 per arm).[35-42] Five trials compared streptokinase with heparin controls[35-38,40]; one trial compared high-dose streptokinase with low-dose

Table V. Summary of study characteristics of miscellaneous trials

Study name	Study arm									No. of patients	Follow-up, months	Ulcers, No. (%)
Monreal[43]	Arm 1	Hy, H, W, C	Hy, W, C	Hy, W, C	Hy, W, C	Hy, W, C	Hy, C	Hy, C	Hy, C	52	36	0
	Arm 2	H, W, C	W, C	W, C	W, C	W, C	C	C	C	48	36	1 (2.1)
Schulman[44,a]	Arm 1	H, W	W, C	W, C	W, C	W, C	C	C		454	120	16 (3.5)
	Arm 2	H, W	W, C	W, C	C	C	C	C		443	120	17 (3.8)
Months since randomization		0	1	2	3	6	12	24	36			

C, Compression stockings; *H*, heparin; *Hy*, hidrosmina; *W*, warfarin.
[a]Some patients also received thrombolytic therapy during acute presentation.

streptokinase[39]; and two trials compared various arms with several different thrombolytics including urokinase, streptokinase, and recombinant tissue plasminogen activator.[41,42] All but one trial[35] used warfarin in the post-thrombotic period for a given duration of treatment (range, 3-12 months). Compression was used in both Schweizer trials,[41,42] but compliance with compression was not indicated. Dose of thrombolytic agent varied greatly between trials, and some did not indicate dosing. Duration of thrombolytic therapy was more consistent, ranging from 5 to 7 days. Six trials reported non-0 values for ulcers,[35,37-39,41,42] for a total of 11 ulcers across all trials. Only in the Arnesen trial did ulcer values differ by >1 between treatment arms.

The three trials comparing streptokinase with heparin with non-0 values for ulcers[35,37,38] were pooled into meta-analysis, illustrated in Fig 5. A total of 114 patients were pooled across all trials for a total ulcer count of 5. Streptokinase groups had lower incidence of venous ulceration after DVT compared with heparin controls (OR, 0.124; 95% CI, 0.021-0.739).

Two studies, illustrated in Table V, did not meet the categorical requirement for compression, LMWH, procedural thrombolysis, or medical thrombolysis. The Monreal trial[43] compared hidrosmina, a venoactive flavonoid, with standard of care vs standard of care alone. The Schulman trial[44] compared standard of care with 6 months of warfarin anticoagulation vs standard of care with 6 weeks of warfarin anticoagulation. Both trials urged participants to use compression for at least 2 years, but compliance was documented only in the Schulman trial. Length of follow-up was 36 months in the Monreal trial and 10 years in the Schulman trial. One ulcer was reported in the Monreal trial. A total of 33 ulcers occurred in the Schulman trial; ulcer rates were similar between the 6-month warfarin cohort (3.5%) and the 6-week cohort (3.8%).

Table VI lists the Cochrane GRADE evidence profiles for all meta-analyzed studies. Most trials received an evaluation of very low quality, whereas procedural thrombolysis trials received an evaluation of low quality.

DISCUSSION

Our study found insufficient evidence to suggest that compression prevents the development of primary venous ulceration in the post-thrombotic period. Patients receiving longer duration of compression treatment appeared to have fewer venous ulcers compared with shorter duration of treatment, but the difference was not significant (Fig 3). Older studies suggested that compression reduces the incidence of PTS.[45] However, a recently published Cochrane meta-analysis review[46] on compression therapy to prevent PTS concluded that compression stockings may reduce the incidence but not severity of PTS. Of note, that study reviewed many of the same trials as this study but focused on broad outcomes including incidence of PTS, incidence of DVT recurrence, patient satisfaction, and quality of life, but it did not specifically address primary venous ulceration. Whereas compression stockings may reduce the incidence of PTS symptoms[47] and accelerate healing in primary venous ulceration,[48] there is insufficient evidence to assess whether compression prevents primary venous ulceration.

Consistent with the assessment of the Cochrane review on compression in PTS, we encountered significant heterogeneity between compression trials.[45] However, because our analysis focused only on the rare event of venous ulceration, heterogeneity was not illustrated appropriately with the I^2 value.[17] A major limitation to the analysis was that the Kahn trial supplied the majority of ulcerative events. Compliance with stockings was reported to be poor in the Kahn trial,[25] but compliance was similar among placebo and compression groups. Duration of treatment and follow-up varied considerably between trials, and in some trials DVT anticoagulation was administered by study investigators, whereas in others it was only documented by study investigators (Kahn et al[25] and Mol et al[26]). However, ulcer rates within each compression trial were similar between compression and control groups (Table I). The Roumen-Klappe study,[27] which compared compression acutely (7-14 days) at time of DVT vs no compression, was held from meta-analysis because of study design; the study was of small sample size and reported no ulcers.

The data on LMWH trials and venous ulceration were conflicting. The Prandoni trial[30] was an older and smaller study that did not follow current guidelines for standard of care; no ulcers occurred in that trial. The Righini trial[21] assessed only DVTs of the distal calf, comparing LMWH with placebo, with a follow-up period of only 3 months; no ulcers occurred. The Gonzalez-Fajardo trial[28] reported no difference in ulcer rates between LMWH and heparin arms, whereas the Hull trial[29] found that extended LMWH treatment after acute DVT significantly reduced the incidence of primary venous ulceration compared with conventional heparin. Two major points of difference exist across these trials: the Gonzalez-Fajardo trial used compression in both arms, whereas the Hull trial did not use compression; and the length of follow-up was markedly longer in the Gonzalez-Fajardo trial (5 years) than in the Hull trial (1 year). The Gonzalez-Fajardo trial did not list the timing of adverse events, and it is possible that the ulcer data are shrouded by a length time bias, given the long follow-up compared with the Hull trial. In the Gonzalez-Fajardo trial, patients who suffered recurrent venous thromboembolism and subsequent venous ulceration are indiscernible from those who developed venous ulceration after the initial DVT; therefore, any protective window of LMWH would not be detectable. An appropriate length of follow-up is crucial to the study of VLU incidence; too short a follow-up will not detect VLUs, whereas too long a follow-up, without careful monitoring

Table VI. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile for trials included in meta-analysis

Certainty assessment				
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**
Compression vs placebo (mean follow-up, 50 months)				
2	Randomized trials	Not serious	Very serious[a]	Serious[b]
Long-term compression vs short-term compression trials (mean follow-up, 24 months)				
2	Randomized trials	Not serious	Very serious[a]	Serious[b]
Procedural thrombolysis vs standard of care (mean follow-up, 27 months)				
2	Randomized trials	Not serious	Very serious[a]	Not serious
Streptokinase vs heparin controls (follow-up range, 7-77 months)				
3	Randomized trials	Not serious	Very serious[a]	Serious[b]

CI, Confidence interval; *OR*, odds ratio.
[a]A large proportion of participants had chronic venous insufficiency at baseline, which limits the ability to detect effects of the intervention.
[b]Venous leg ulcers were not a primary or secondary outcome in the trials.
[c]The sample sizes for detecting a rare event like venous leg ulcers were low.

of the progression of baseline CVD or recurrent thrombosis, can obscure the classification of VLUs as secondary to post-thrombotic syndrome or secondary to the progression of baseline CVD. In the future investigation of VLUs, a standardized length of follow-up, likely between 2 and 10 years, should be established to improve the reliability with which VLUs are detected, reported, and classified according to etiology.

In addition, LMWHs differ in pharmacokinetic and anticoagulant profiles and should not be clinically interchangeable. Tinzaparin, the LMWH of choice in the Hull trial,[29] is prepared by enzymatic hydrolyzation and has the highest molecular weight of the LMWHs. It is known to induce greater release of tissue factor pathway inhibitor, which has potent antiangiogenic effects outside of its anticoagulant properties, making it especially efficacious in management of malignant neoplasms.[49] Currently, the data on whether anticoagulant choice in the post-DVT period protects against venous ulceration are extremely limited.

We did not find evidence that procedural thrombolysis with catheter-directed thrombolysis (with or without angioplasty and stenting) reduced incidence of venous ulceration. Fewer ulcers occurred in procedural thrombolysis participants[13] compared with standard of care patients,[20] but the effect was not significant (OR, 0.6545; 95% CI, 0.327-1.31). The procedural thrombolysis trials were generally of higher quality and of more consistent study design with respect to adherence to standard of care including use of compression, length of follow-up, and sample size (Table III). Further RCTs with sufficient length of follow-up are required to adequately assess the effect of procedural thrombolysis on venous ulceration.

Medical thrombolysis with streptokinase conferred a protective effect on venous ulceration compared with standard heparinization. However, this analysis should be interpreted with great caution. The medical thrombolysis trials were largely older and of poorer study quality for the reasons of small sample size, lack of standard of care, and inconsistent dosing of thrombolytics. There was significant heterogeneity between trials concerning use of warfarin and compression and study follow-up. Ulceration rates were similar between arms of most trials, except for the Arnesen study, in which three more ulcers occurred in the heparin group compared with the streptokinase arm. However, anticoagulation was not extended past the initial streptokinase or heparin treatment, and the absolute ulcer rate in the heparin group was markedly high (16.7%), indicating poor overall outcomes.[35] Most important, systemic thrombolytics are now considered an outmoded pharmacotherapy for DVTs as the only current indication for thrombolytics in DVT treatment is local application with catheter-directed modalities.

The Schulman trial[44] on duration of warfarin treatment after DVT suggests that extended warfarin treatment past 6 weeks does not protect against venous ulceration. Whereas this study was well designed and of considerable sample size (Table V), the follow-up period was

Table VI. Continued.

Certainty assessment		No. of patients		Effect	
Imprecision	Other considerations	Intervention	Comparison	Peto OR (95% CI)	Certainty
Compression vs placebo (mean follow-up, 50 months)					
Not serious	None	18/505 (3.6%)	19/492 (3.9%)	0.915 (0.475-1.765)	⊕◯◯◯ Very low
Long-term compression vs short-term compression trials (mean follow-up, 24 months)					
Not serious	None	0/690 (0.0%)	3/693 (0.4%)	0.136 (0.014-1.310)	⊕◯◯◯ Very low
Procedural thrombolysis vs standard of care (mean follow-up, 27 months)					
Not serious	None	13/427 (3.0%)	20/447 (4.5%)	0.677 (0.338-1.358)	⊕⊕◯◯ Low
Streptokinase vs heparin controls (follow-up range, 7-77 months)					
Very serious[c]	Inconsistent dosing of thrombolytics	0/58 (0.0%)	5/56 (8.9%)	0.124 (0.021-0.739)	⊕◯◯◯ Very low

extremely long, which could be subjecting the study to the same length time bias as discussed in the Gonzalez-Fajardo trial. We did not find any studies related to newer oral anticoagulants, such as factor Xa or direct thrombin inhibitors. In the Monreal study[43] on hidrosmina, a venoactive flavonoid, one ulcer occurred in the control arm and none occurred in the experimental arm, but sample size was relatively small (48-52/arm).

This study was limited by intertrial heterogeneity concerning duration of treatment and follow-up, use of compression and other ancillary treatments, adherence to compression therapy, and adherence to standard of care guidelines. Additional limitations include evaluation of a metric that was not the primary end point of study trials, evaluation of a rare event in studies of modest sample size, and inability to properly quantitate study heterogeneity given the rarity of the study end point. The GRADE evidence profile for all trials was very low except for procedural thrombolysis trials, for which it was low. Another major limitation is that most included trials did not provide adequate documentation of pre-existing CVD, which is a potential confounder for VLU detection in that the effect of DVT treatment in preventing VLUs is difficult to detect with high baseline risk for ulceration.

CONCLUSIONS

Whereas compression stockings appear to reduce incidence of PTS,[46] we found insufficient evidence to suggest that compression reduces the incidence of venous ulceration, the end point of venous insufficiency.[9] Compression stockings do confer treatment benefits in the post-DVT period, but current data from DVT RCTs are much too limited to answer whether protection against venous ulceration can be achieved with current treatments. Considering that venous ulceration is a relatively rare event, large, multicenter RCTs or long-term registries investigating PTS and VLUs as a primary outcome are required to inform treatment decisions regarding prevention of venous ulceration. Further research should be conducted of anticoagulant treatment in the acute DVT setting, including type and duration of anticoagulation, specifically with LMWHs and procedural thrombolysis.

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AUTHOR CONTRIBUTIONS

Conception and design: BD, JJ, AL, HLT
Analysis and interpretation: BD, JJ, AL, HLT
Data collection: BD, JJ, HLT
Writing the article: BD, JJ
Critical revision of the article: BD, JJ, AL, HLT
Final approval of the article: BD, JJ, AL, HLT
Statistical analysis: BD, JJ, HLT

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BD and JJ contributed equally to this article and share co-first authorship.

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APPENDIX (online only).

Search strategy algorithm.

PubMed	(((((((((("Venous Insufficiency"[Mesh] OR venous insufficiency))) OR (((venous valve[MeSH Terms]) OR (venous reflux)))) OR (("Venous Thrombosis"[Mesh] OR (deep venous thrombosis)))) OR ((("Edema"[Mesh]) AND "Leg"[Mesh])) OR (leg edema))) OR ((stasis dermatitis) OR (venous dermatitis))) OR (((varicose vein[MeSH Terms]) OR (varicose vein))) OR ((("Postthrombotic Syndrome"[Mesh] OR ((Post thrombotic Syndrome) OR (Postthrombotic Syndrome) OR (Post-thrombotic Syndrome))) OR (("Lipodermatosclerosis" [Supplementary Concept]) OR Lipodermatosclerosis) Filters: Randomized Controlled Trial; Humans; English; Hebrew; Spanish
Embase	'leg edema'/exp OR 'leg edema' OR 'chronic vein insufficiency'/exp OR 'chronic vein insufficiency' OR 'statis dermatitis' OR 'venous dermatitis' OR 'leg varicosis'/exp OR 'leg varicosis' OR 'lipodermatosclerosis'/exp OR 'lipodermatosclerosis' OR 'venous reflux'/exp OR 'venous reflux' OR 'postthrombosis syndrome'/exp OR 'postthrombosis syndrome' OR 'deep vein thrombosis'/exp OR 'deep vein thrombosis' AND [embase]/lim NOT [medline]/lim AND 'randomized controlled trial'/de AND ([english]/lim OR [hebrew]/lim OR [spanish]/lim) AND [humans]/lim AND ('chronic vein insufficiency'/de OR 'deep vein thrombosis'/de OR 'leg edema'/de OR 'postoperative complication'/de OR 'postthrombosis syndrome'/de OR 'side effect'/de OR 'thromboembolism'/de OR 'thrombosis'/de OR 'vein thrombosis'/de OR 'venous thromboembolism'/de