CLINICAL RESEARCH STUDY

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Compression Stockings for Preventing the Postthrombotic Syndrome in Patients with Deep Vein Thrombosis

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ABSTRACT

OBJECTIVE: We conducted a systematic review and meta-analysis to address benefits and harms of using elastic compression stockings after lower-extremity deep vein thrombosis.

METHODS: We searched 7 electronic databases through January 15, 2015, including randomized controlled trials (RCTs)/quasi-randomized trials reporting on elastic compression stocking efficacy on postthrombotic syndrome incidence, recurrent venous thromboembolism, mortality, and acute pain after deep vein thrombosis. Two reviewers independently screened records, extracted data, assessed risk of bias, and assessed confidence in effect estimates using Grading of Recommendations Assessment, Development, and Evaluation methodology. We applied random-effects meta-analysis models.

RESULTS: We included 5 RCTs (n = 1418) reporting on postthrombotic syndrome. The hazard ratio (HR) for postthrombotic syndrome with elastic compression stockings was 0.69 (95% confidence interval [CI], 0.47-1.02). We have very low confidence in this estimate due to heterogeneity and inclusion of unblinded studies at high risk of bias. Excluding high risk of bias studies, a single large RCT at low risk of bias provided moderate-quality evidence of no effect on postthrombotic syndrome (HR 1.00; 95% CI, 0.81-1.24). Moderate-quality evidence including all 5 studies suggests no effect of elastic compression stockings on recurrent venous thromboembolism (relative risk [RR] 0.88; 95% CI, 0.63-1.24) or mortality (RR 1.00; 95% CI, 0.73-1.37, 5 studies). Moderate-quality evidence from one large RCT does not suggest effect on acute pain after deep vein thrombosis.

CONCLUSIONS: The highest-quality evidence available suggests no effect of elastic compression stockings on postthrombotic syndrome or pain relief, from a single large RCT. However, results for preventing postthrombotic syndrome differ substantially across studies, and future guideline updates should reflect uncertainty about treatment effects. Elastic compression stockings are unlikely to prevent death or recurrent venous thromboembolism.

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KEYWORDS: Compression stockings; Deep vein thrombosis; Meta-analysis; Postthrombotic syndrome

The application of elastic compression stockings after deep vein thrombosis of the leg to prevent the development of postthrombotic syndrome is a widespread practice, and recommended in several recent guidelines.[1-4]

Although postthrombotic syndrome definitions vary,[5-7] it is generally described as a condition that follows symptomatic deep vein thrombosis and is associated with swelling and

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edema of the leg, itching, ectatic veins, feeling of heaviness, cramps, pain, and paresthesias.[5,8-12] Several diagnostic instruments for postthrombotic syndrome exist, including the Ginsberg[5] and Villalta[12,13] scales. The incidence of postthrombotic syndrome following deep vein thrombosis varies widely in different reports, from about 20% to more than 50%[5,12,14-17]; the difference is due at least in part to use of different diagnostic instruments.

Mechanisms of elastic compression stocking effect may include improved venous return through external compression,[18] with associated reduction in edema and swelling in the extremity and improved microcirculation.[12,19] Elastic compression stockings may be individually tailored or off the rack,[8] knee or thigh high, and generally exert a pressure of around 20-40 mm Hg.[9] Although stockings are reportedly well tolerated,[12] they may be cumbersome. Patients may experience treatment durations of years as a significant burden.

Two randomized controlled trials (RCTs) have suggested that elastic compression stockings may reduce the incidence of postthrombotic syndrome by about 50%.[12,20] In a 2010 meta-analysis, Musani et al[21] concluded that venous compression is likely to be effective, although they stated that more research was needed. A recent RCT contradicts this conclusion.[8] We seek to explain the difference in results and provide the best available estimate of effects.

CLINICAL SIGNIFICANCE

- Elastic compression stockings are applied to prevent postthrombotic syndrome after lower-extremity deep vein thrombosis.
- Treatment with compression stockings may last for years, constituting a significant burden for patients.
- We find that the highest-quality evidence available does not indicate an effect of compression stockings to prevent the postthrombotic syndrome, nor on the recurrence of thrombosis, mortality, or pain in the acute phase of deep vein thrombosis.

METHODS

We prespecified eligibility criteria, literature searches, methods of risk-of-bias assessment, and intended analysis methods, including subgroup analyses. The protocol is publicly available in the PROSPERO database.[22]

Literature Searches

We searched PubMed, Ovid MEDLINE and Ovid EMBASE (including EMBASE Classic), and Cochrane CENTRAL for relevant primary studies through January 15, 2015. We excluded MEDLINE-indexed journals in EMBASE searches. We searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the National Health Service Economic Evaluation Database, and the National Health Service Health Technology Assessment Database for previous reviews on the topic, and screened their bibliographies for relevant primary studies.

We performed searches using population and intervention free-text synonyms and database-specific controlled vocabulary, applying no date, language, or outcome restrictions, nor any filters. **Appendix Table 1** (available online) presents full search strategies. One author (CFB) developed the search strategies; medical librarians subsequently reviewed them and confirmed their comprehensiveness.

Study Selection

We included RCTs and quasi-randomized trials (ie, based on birth date, order of enrollment into study) with patients having experienced a symptomatic lower-extremity deep vein thrombosis, objectively verified by ultrasonography or another suitable radiographic modality. Patients must either have started treatment with elastic compression stockings within 3 months of the deep vein thrombosis, or if stocking treatment was begun after 3 months, they must have been symptom free at treatment initiation. We included only studies reporting either of the patient-important outcomes postthrombotic syndrome, venous thromboembolism recurrence or death; or one outcome not prespecified in the protocol: pain in the acute phase after deep vein thrombosis.

We de-duplicated search outputs using EndNote X7.[23] In the first round of screening, reviewers (CFB and AK) excluded obviously irrelevant records after independent duplicate examination of title and abstract. We retrieved full texts for citations deemed potentially eligible by at least one reviewer, and screened them in duplicate using the Web-based screening software Covidence.[24] Disagreements were resolved through discussion.

Data Extraction and Quality Assessment

Reviewers (CFB and either POV or AK) extracted data in duplicate and independently, using standardized forms and resolving disagreements through discussion. We extracted data on participant characteristic, intervention, and control; timing of start of treatment; follow-up time; and statistical data for the prespecified outcomes, important adverse effects, and pain in the acute phase after deep vein thrombosis. Data on postthrombotic syndrome were recorded as dichotomous or survival data, or treatment effects on a relevant diagnostic instrument. For studies not presenting hazard ratios (HRs) for postthrombotic syndrome, we extrapolated these from Kaplan-Meier plots where available using the method of Parmar et al.[25] Two reviewers (CFB and POV) independently assessed risk of bias of each study for each outcome using the Cochrane risk-of-bias tool[26] (**Appendix Table 2**, available online).[5,8,12,20,27-33]

Data Synthesis

As most studies presented treatment effect of elastic compression stockings on the development of post-thrombotic syndrome after deep vein thrombosis as survival data, we chose a generic inverse variance random-effects meta-analysis model to pool HRs for postthrombotic syndrome. For other dichotomous outcomes, we performed a complete case analysis and a series of sensitivity analyses with progressively more stringent imputations of event rates for patients lost to follow-up.[34,35] The impact of these assumptions about missing data on the point estimates and their precision determined whether we rated down for risk of attrition bias.[34] We also re-analyzed time-to-event data as relative risks of developing events during follow-up and performed imputed case analyses to test the potential impact of attrition. We pooled relative risks for dichotomous outcomes (death and venous thromboembolism recurrence) using a Mantel-Haenszel random-effects model. We assessed heterogeneity by calculating a P value for χ^2 and an I^2 statistic, and conducted subgroup analyses for timing of randomization, localization of the deep vein thrombosis, and application of blinding as prespecified in the review protocol. We used RevMan 5.3[36] for the primary analysis, and Microsoft Excel[37] with the add-on MetaXL[38] for supplementary sensitivity analyses. We generated anticipated absolute effects for patient-important outcomes by applying the final effect estimates from our review to baseline risk estimates from observational studies[39] or control arms from relevant studies.[8,12] We assessed confidence in estimates of treatment effect in duplicate, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[40] approach.

RESULTS

Of 2522 records remaining after de-duplication, we reviewed 94 in full text, of which 7 proved eligible (**Figure 1**). **Appendix Table 3** (available online) presents bibliographical details of excluded studies and reasons for exclusion. One author (CFB) examined bibliographies of 68 previous reviews and commentaries, but identified no further primary studies.

Table 1[5,8,12,20,27-29,41,42] presents characteristics of the included studies. Five studies were not blinded[12,20,27-29] ;2[5,8] blinded patients and personnel using stockings assumed to have no treatment effect. Six studies assessed post-thrombotic syndrome as the primary outcome[5,8,12,20,27,29]; one reported only venous thromboembolism recurrence and death.[28] Three studies provided standard care, including low-molecular-weight heparin or vitamin K antagonists for periods between 6 months[5,28] and 1 year[27] before patients were randomized. For 2 of these,[5,27] standard care included elastic compression stockings use; the remaining study[28] did not describe whether standard care included stockings. Five different scoring instruments were used for diagnosing postthrombotic syndrome.

Although not all studies applied all criteria, they typically excluded patients with preexisting venous disease or postthrombotic syndrome, contraindications to elastic compression stockings, current or previous stocking use, short life expectancy, and anticipated difficulties with treatment and follow-up compliance. One study did not specify exclusion criteria.[28] A planned formal analysis for assessing publication bias was not feasible due to the scarcity of studies.

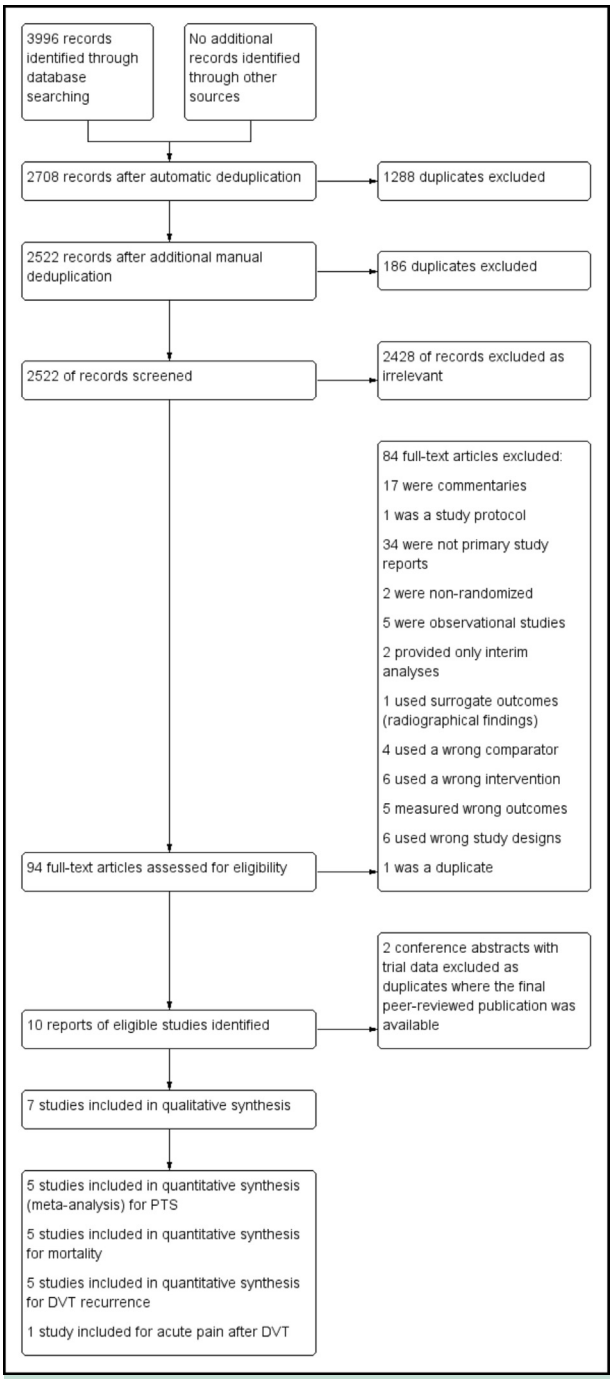

Figure 1 Study flow diagram.

Development of Postthrombotic Syndrome

Five studies (n = 1418)[8,12,20,27,29] reported postthrombotic syndrome incidence as survival data, of which 3[8,12,27]

Table 1 Characteristics of Included Studies

Study, y (Reference)	Patient Characteristics: Patients (n)	Eligible Deep Vein Thrombosis Events	Mean/Median Age; Intervention/Control	% Men	Intervention	Control	Intervention Start	Follow-Up Years	Postthrombotic Syndrome Instrument
Aschwanden et al, 2008[27]	169	Popliteal vein or more proximal, first-time deep vein thrombosis	64.1/53.8	58.6	26.3-36.1 mm Hg elastic compression stockings, off-the-rack bought by patients	No treatment	6 mo after deep vein thrombosis	Mean 3.2 (intervention)/ 2.9 (control)	CEAP[41]
Belcaro et al, 1993[28]	116*	Not stated	46.0/45.7	45.9	Elastic compression stockings, not further specified†	No treatment	Within 7 mo from deep vein thrombosis	3, mean follow-up unclear	N/A†
Brandjes et al, 1997[20]	194	Popliteal vein or more proximal, first-time deep vein thrombosis	60/59	55.9	Custom-made 21-40 mm Hg elastic compression stockings, exchanged every 6 mo	No treatment	2-3 wk after deep vein thrombosis diagnosis	Median 6.3 across groups	Brandjes
Ginsberg et al, 2001[5]	47‡	Popliteal vein or more proximal, first-time deep vein thrombosis	62.0/60.5	55.3	20-30 mm Hg elastic compression stockings, exchanged every 6 mo	Elastic compression stockings 1-2 sizes too large	1 y after deep vein thrombosis	Mean 4.6/4.9	Ginsberg
Jayaraj et al, 2015[29]	69	Deep vein thrombosis proximal to the calf veins, first-time deep vein thrombosis	48/47	50.7	30-40 mm Hg elastic compression stockings, exchanged every 4 mo	No treatment	Within 48 h of deep vein thrombosis	2, mean not explicitly stated	Villalta and VCSS[42]
Kahn et al, 2014[8]	806	Popliteal vein or more proximal, first-time deep vein thrombosis	55.4/54.8	59.9	30-40 mm Hg elastic compression stockings, exchanged every 6 mo	Sham 5 mm Hg elastic compression stockings	Within 2 wk of deep vein thrombosis	2 across groups	Ginsberg and Villalta

Table 1 Continued

Study, y (Reference)	Patient Characteristics								
	Patients (n)	Eligible Deep Vein Thrombosis Events	Mean/Median Age; Intervention/Control	% Men	Intervention	Control	Intervention Start	Follow-Up Years	Postthrombotic Syndrome Instrument
Prandoni et al, 2004[12]	180	Popliteal vein or more proximal, first-time deep vein thrombosis	60.1/62.0	42.8	Off-the-rack 30-40 mm Hg elastic compression stockings, exchanged every 6 mo	No treatment	Prior to hospital discharge after deep vein thrombosis, average 1 wk (range 5-10 d)	5, mean not explicitly stated	Villalta

CEAP = Clinical – Etiology – Anatomy – Pathophysiology classification; VCSS = Venous Clinical Severity Score.
*The study applied a 2 × 2 factorial design with the platelet inhibitor indobufen. We excluded the groups having received indobufen as a co-intervention from our analysis as symptomatic venous thromboembolism relapse rates were zero in both these groups, correction for indobufen as an effect modifier is thus impossible.
†The study did not report postthrombotic syndrome as an outcome.
‡The study was conducted in parallel with an observational study of the incidence of postthrombotic syndrome in a group not treated with elastic compression stockings after deep vein thrombosis and a study of stocking efficacy in treating established postthrombotic syndrome; eligible patients were allocated to the respective studies according to prespecified criteria.

presented HRs and 2[20,29] Kaplan-Meier curves. From one of the latter,[20] we extrapolated an HR from the curve for mild to moderate postthrombotic syndrome, which we construed as the overall cumulative incidence because patients with severe postthrombotic syndrome would also fulfill the mild-to-moderate criteria. The other[29] provided several cutoff points for the timing of the first postthrombotic syndrome diagnosis; we computed an HR from the curve for postthrombotic syndrome diagnosed, at the earliest, at 6 months to avoid confusion of postthrombotic syndrome and symptoms in the acute phase of deep vein thrombosis.[43]

Of 4 unblinded studies, 2 reported a significant reduction in postthrombotic syndrome rates in the elastic compression stocking group, with HRs of 0.42 (95% CI, 0.26-0.69, n = 194)[20] and 0.47 (95% CI, 0.28-0.79, n = 180)[12] (unadjusted estimate prior to correcting for baseline variables; correction yielded similar results), and a third an apparent reduction but with very wide CIs, including an increase in risk (HR 0.60; 95% CI, 0.28-1.28, n = 169).[27] One small, unblinded study[29] did not show effect (HR 1.05; 95% CI, 0.71-1.56 on the Villalta scale; HR 0.91; 95% CI, 0.37-2.26 on the Venous Clinical Severity Score [VCSS], n = 69); neither did a blinded study with a larger sample size (HR 1.13; 95% CI, 0.73-1.76 on the Ginsberg scale; HR 1.00; 95% CI, 0.81-1.24 on the Villalta scale, n = 806).[8]

One blinded study[5] (n = 47) was uninformative, as the sample size was small and the event rate low due to a stricter postthrombotic syndrome definition. We deemed that applying a continuity correction would be inappropriate and introduce bias due to the low event rate, and that an HR was not computable; we thus excluded this RCT from the meta-analysis. When we re-analyzed postthrombotic syndrome event data as a binary outcome in sensitivity analyses, this study had only a marginal impact on the pooled estimate.

The pooled HR from the meta-analysis for postthrombotic syndrome was 0.69 (95% CI, 0.47-1.02), using Villalta scale estimates where available[43] (**Figure 2**). Using Ginsberg and Venous Clinical Severity Score[42] estimates from the studies that additionally provided these[8,29] gave similar results (HR 0.69; 95% CI, 0.45-1.07 and 0.64; 95% CI, 0.41-1.00, respectively).

Inspection of the data and a formal statistical test indicated substantial heterogeneity (**Figure 2**). We performed a subgroup analysis for unblinded vs blinded studies; even within the unblinded studies group there was substantial heterogeneity (**Figure 2**). A pooled estimate for the unblinded studies (HR 0.60; 95% CI, 0.37-0.98) differed markedly from the only blinded RCT[8] included in the analysis (HR 1.00; 95% CI, 0.81-1.24), a difference unlikely to be explained by chance ($P = .06$) (**Figure 2**).

We conducted a prespecified subgroup analysis for studies randomizing patients immediately vs after a delay >3 months, to investigate whether an effect may have been diluted by prerandomization elastic compression stocking use. We found no difference between subgroups (χ^2 0.12, $df = 1$, $P = .73$, I^2 0%), but power was low as only one study with delayed treatment[27] was included. We

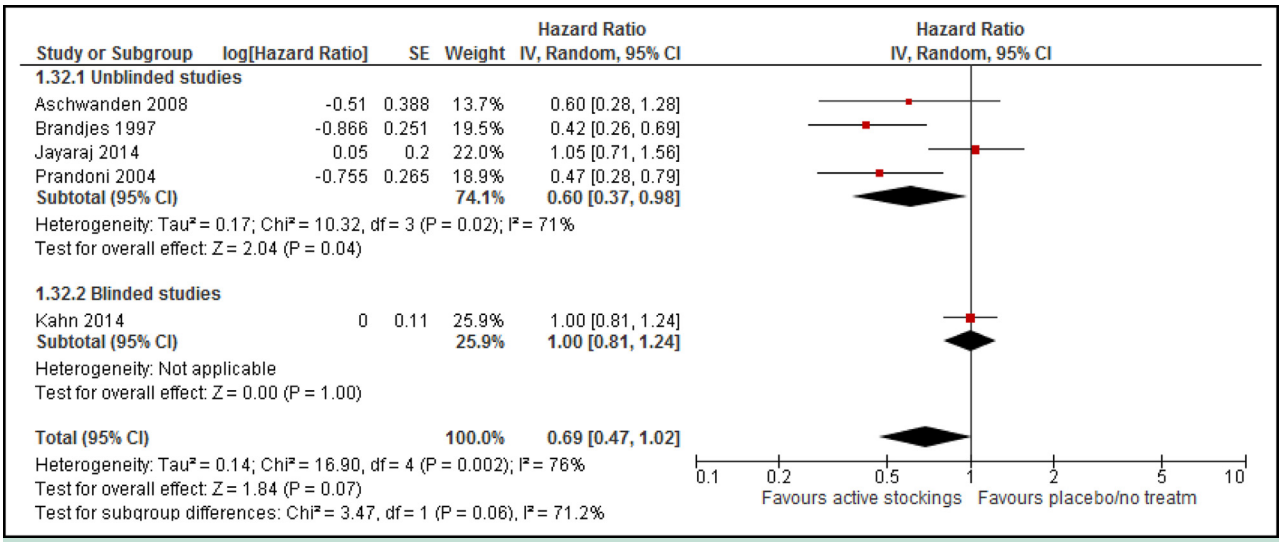

Figure 2 Meta-analysis of hazard ratio for postthrombotic syndrome. CI = confidence interval.

prespecified a subgroup analysis for index deep vein thrombosis location; this was not applicable, as all studies reporting on postthrombotic syndrome included only patients with deep vein thrombosis proximal to the popliteal vein.

Venous Thromboembolism Recurrence

Five studies[5,8,12,27,28] reported on venous thromboembolism recurrence (n = 1465). One study[28] found a preventive effect of elastic compression stockings on recurrent symptomatic venous thromboembolism within 3 years (relative risk [RR] 0.22; 95% CI, 0.05-0.93, n = 116). All other studies failed to detect differences between elastic compression stockings and control in venous thromboembolism recurrence.

Because no study presented survival data, we computed relative risks until end of follow-up and found consistent results suggesting little or no effect of elastic compression stockings on venous thromboembolism recurrence (**Figure 3**) (RR 0.88; 95% CI, 0.63-1.24). There was one outlier,[28] which we had rated at high risk of bias. A sensitivity analysis did not reveal any significant impact of this study on the pooled estimate, which was also robust in a series of imputed case analyses of the impact of missing data.

Death

As for venous thromboembolism recurrence, we computed relative risks of death (**Figure 4**) for the 5 studies (n = 1396) that reported on this outcome. Results suggested no effect of elastic compression stockings on all-cause mortality (RR 1.00, 95% CI 0.73-1.37), and were consistent across studies although follow-up time varied, as well as in sensitivity analyses for missing data.

Pain in the Acute Phase after Deep Vein Thrombosis

Only one included study reported on the effect of elastic compression stockings on pain in the acute phase after deep vein thrombosis.[44] Patients reported pain on a numerical rating scale from 0 to 10; where 0 was no pain and 10 was worst possible pain. Difference in pain ratings between patients using active and placebo stockings was not detected at baseline (difference in means 0.20; 95% CI, −0.26 to

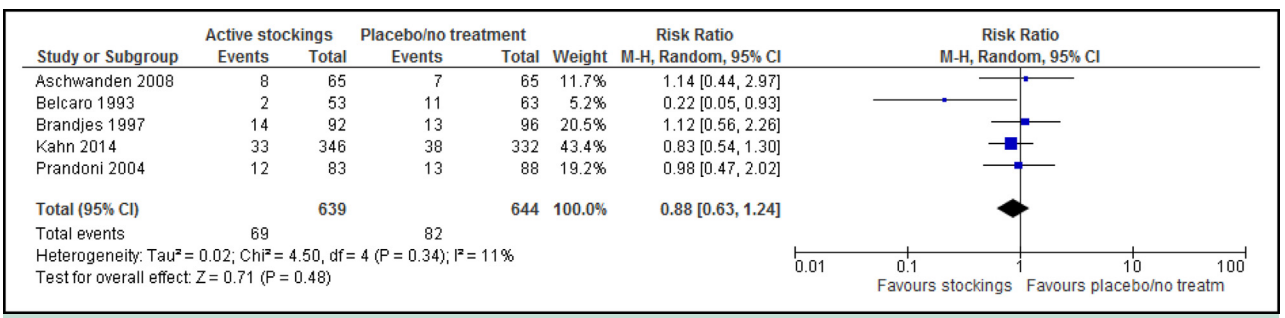

Figure 3 Meta-analysis of relative risk of venous thromboembolism recurrence. Complete case analysis. CI = confidence interval.

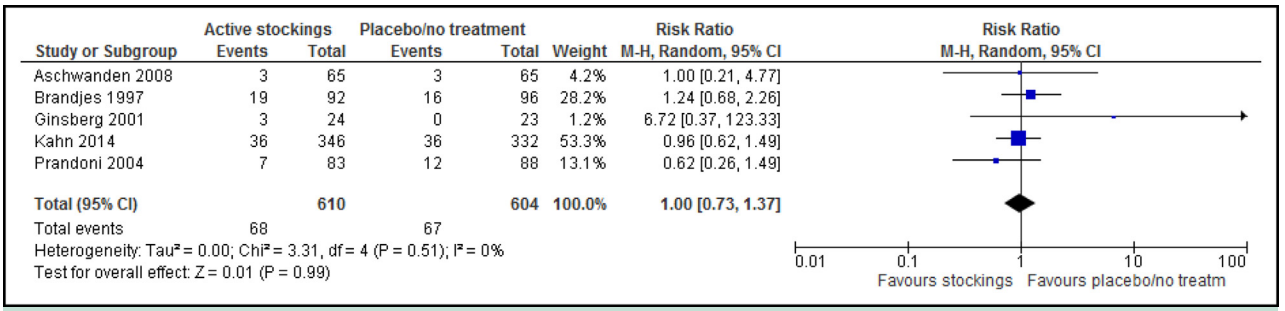

Figure 4 Meta-analysis of relative risk of death. Complete case analysis. CI = confidence interval.

0.66), 14 days (0.08; 95% CI, −0.29 to 0.45), 30 days (−0.18; 95% CI, −0.53 to 0.18), or 60 days (−0.27; −0.56 to 0.03).

Adverse Events

Studies reported only minor adverse advents, which were rare. One study at high risk of bias reported no events[28] across groups; one study reported itching in 6% of active group patients and made no statement about events in the untreated group.[12] The large RCT using placebo stockings[8] reported few events in both groups, and no difference between groups (itching or rash in 2% in both groups). Three studies did not quantify minor events. One study made no mention of adverse events.[29] We could not pool effect estimates statistically because the studies either had no control group events or did not report them.

Summary of Findings

In Table 2[8,12,16,28,29,39,43,45,46] we present a summary of our findings, providing estimates of absolute effects of elastic compression stockings on our included outcomes, and GRADE assessments of the quality of evidence.[40] For postthrombotic syndrome incidence, we have very low confidence in the estimate from the meta-analysis due to serious inconsistency, imprecision, and serious risk of bias. If, however, we dismiss the studies at high risk of bias, we are left with one study that provides moderate-quality evidence that there is no effect of elastic compression stockings on postthrombotic syndrome, rating evidence quality down for imprecision as the CI includes appreciable potential benefit from elastic compression stockings.[8] If one believed that the placebo stockings had a biological effect in reducing postthrombotic syndrome, one might rate down further due to indirectness. Our estimate of absolute effects on postthrombotic syndrome is based on this study as we find it to provide the highest-quality evidence available.

DISCUSSION

The available RCTs showed inconsistent results of the impact of elastic compression stockings on postthrombotic syndrome. Several of the studies we classified as being at high risk of bias showed a large effect,[12,20,27] while the one large RCT at low risk of bias showed no effect.[8] Commentaries have suggested that the timing of the start of stocking treatment in the large RCT, as well as the failure to provide stockings that were made to measure, may explain the discrepant results.[47,48] The low-risk-of-bias study does not, however, differ substantially in these regards from the majority of the other studies starting treatment in the acute phase (Table 1).

We identify 2 main hypotheses that may explain the discrepancies:

1. Earlier studies present inflated estimates due to methodological flaws, especially lack of blinding.[12,20,27]
2. There is a therapeutic effect of the 5-mm Hg compression sham stockings in the large study at low risk of bias.[8]

A relatively poor compliance in the large study at low risk of bias[8] (55.6% of patients reported using stockings >3 days per week at end of follow-up) could threaten the applicability of the results. This issue has caused considerable controversy in the research community.[47,49] However, given the high cumulative incidence of postthrombotic syndrome in the cohort (up to 52% using Villalta criteria, 12%-14% using Ginsberg criteria), we find that the study would likely have detected a substantial underlying effect despite the limited compliance. Indeed, if the approximate 50% hazard reduction from the 3 unblinded studies showing effect is applied to compliant patients in the blinded study with 50% compliance, one would anticipate a 25% reduction in hazard. Moreover, the authors report that frequent (more than 3 days per week) stocking users had no better results for the postthrombotic syndrome outcome in a prespecified subgroup analysis; a post hoc analysis similarly showed that daily users were no better off.

We have serious concerns about the unblinded studies[12,20,27]; such designs may inflate treatment effects.[50,51] This effect is especially likely to be prominent if outcome assessment is wholly or partially subjective (such as symptom and sign assessment on a clinical rating instrument).[52] Formal assessment of unmasking at the end of the low-risk-of-bias study[8] did not indicate that unmasking had taken place in the placebo group; this indicates that blinded designs are indeed feasible when studying elastic compression stocking efficacy.

Table 2 Summary of Findings

Outcome	Estimated Absolute Effects from Studies (95% CI)			Relative Effect (95% CI)	Number of Participants (Studies), Follow-Up	Quality of Evidence (GRADE)	Comments
	No Treatment or Placebo	Elastic Compression Stockings	Difference with Elastic Compression Stockings				
Postthrombotic syndrome, overall cumulative incidence at 2 y, effect estimate from single low-risk-of-bias study[8]	491 per 1000*	491 per 1000 (398-609)	0 fewer per 1000 (93 fewer-118 more)	HR 1.00 (0.81-1.24)‡	806 (1), 2 y	⊕ ⊕ ⊕ ⊖ MODERATE	Rated down for imprecision, wide confidence interval.
Mortality at 2 y	108 per 1000†	108 per 1000 (78-147)	0 fewer per 1000 (29 fewer-40 more)	RR 1.00 (0.73-1.37)	1396 (5), 2-7 y	⊕ ⊕ ⊕ ⊖ MODERATE	Not rated down for unblinded studies as this was not expected to influence on the assessment of this outcome. Rated down for imprecision, wide confidence interval.
Venous thromboembolism relapse at 3 y	196 per 1000§	172 per 1000 (123-243)	24 fewer per 1000 (73 fewer-47 more)	RR 0.88 (0.63-1.24)	1465 (5), 2-7 y	⊕ ⊕ ⊕ ⊖ MODERATE	One study at high risk of bias showed diverging results from the others, but a sensitivity analysis did not show any impact of the exclusion or inclusion of this study on the final estimate. Rated down for imprecision, wide confidence interval.

Table 2 Continued

Outcome	Estimated Absolute Effects from Studies (95% CI)			Relative Effect (95% CI)	Number of Participants (Studies), Follow-Up	Quality of Evidence (GRADE)	Comments
	No Treatment or Placebo	Elastic Compression Stockings	Difference with Elastic Compression Stockings				
Pain on numeric rating scale (0-10) at 14 d	5.38 of 10‖	5.18 of 10 (5.12-5.84)	0.20 less out of 10 (0.26 less-0.66 more)	4% reduction in pain score (5% less-12% more)¶	806 (1), 60 d	⊕ ⊕ ⊕ ⊖ MODERATE	Only one study reported pain as an outcome. Rated down for indirectness due to use of placebo stockings in control group.
Adverse events	Studies reported scarcely on adverse events and rarely quantified them, but the absence of major adverse events was consistent across studies. One study reported itching in 6% of patients using elastic compression stockings,[12] whereas one reported 2% across groups,[8] and one reported zero events.[28] One study did not mention adverse events.[29] Due to scarce reporting, we do not provide a pooled estimate.					⊕ ⊕ ⊖ ⊖ LOW	Low incidence of adverse events across studies, but rated down for selective reporting and imprecision

CI = confidence interval; HR = hazard ratio; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; RR = relative risk.

*We have chosen the postthrombotic syndrome incidence of the untreated arm of the study by Prandoni et al[12] as basis for the control group absolute risk, this study does not use placebo stockings that may be suspected to impact on the estimate. The study uses the Villalta scale for postthrombotic syndrome assessment, as recommended by the International Society for Thrombosis and Haemostasis.[43] Observational studies have yielded different incidences, but are not commonly performed on cohorts not treated with elastic compression stockings.[16,45]

†Mortality baseline estimates are from the control arm of the study by Kahn et al,[8] which we found to be a high-quality study at low risk of bias, it also has a large sample size. The estimate does not differ substantially from the other included studies.

‡Estimate from analysis using Villalta scale for postthrombotic syndrome diagnosis, which is more precise than the Ginsberg scale estimate due to a higher event rate.

§Estimate from prospective cohort study by Prandoni et al[39] with 1626 patients. Heit et al[46] reported similar findings.

‖Estimate from placebo arm of the only included study reporting on this outcome.

¶Absolute reduction in pain score for elastic compression stocking group converted to percentage of control group score.

Whether the lightweight presumed placebo compression in the low-risk-of-bias study has a therapeutic effect could be further investigated; this applies both for postthrombotic syndrome and for acute pain after deep vein thrombosis. The lack of uniform application of postthrombotic syndrome diagnostic criteria must also be addressed to allow consistent comparisons of study results for the future; in an effort toward standardization, the International Society on Thrombosis and Haemostasis has recommended the Villalta scale for research purposes.[43]

Our review is limited by the differing postthrombotic syndrome definitions across studies, heterogeneity of included study results, and varying follow-up times across studies. We have, however, examined reasons for the heterogeneity, and present alternative interpretations of the data in a transparent way. Other strengths of our review include a thorough literature search, and thorough evaluation of risk of bias. We also conducted extensive sensitivity analyses to assess the potential impact of missing data, and found little influence.

CONCLUSIONS

The differing results across studies suggest that the decision to use elastic compression stockings may be value and preference dependent. Patients who find stockings onerous and place a low value on a very uncertain benefit are likely to decline treatment. Those who find wearing stockings of little burden and place a high value on a very uncertain benefit, or experience symptom relief from stocking use, are likely to choose treatment. Prominent guidelines[1-4] currently recommend the routine application of elastic compression stockings after deep vein thrombosis; the uncertainty about treatment effects should be reflected in future updates.

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APPENDIX

Supplementary tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.11.031.

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Authorship: All authors had access to all data and a role in writing the manuscript.

Appendix Table 1 Literature Search Strategies

Line #	PubMed	Ovid MEDLINE	Ovid EMBASE	Cochrane Library	CRD/York Databases
1	veno* thrombo*	veno* thrombo*.mp.	veno* thrombo*.mp.	veno* thrombo*	veno* thrombo*
2	DVT	DVT.mp.	DVT.mp.	DVT	DVT
3	deep vein thrombos*	deep vein thrombos*.mp.	deep vein thrombos*.mp.	deep vein thrombos*	deep vein thrombos*
4	VTE	VTE.mp.	VTE.mp.	VTE	VTE
5	thromboemboli*	thromboemboli*.mp.	thromboemboli*.mp.	thromboemboli*	thromboemboli*
6	tromboemboli*	tromboemboli*.mp.	tromboemboli*.mp.	tromboemboli*	tromboemboli*
7	postthrombo* syndrom*	postthrombo* syndrom*.mp.	postthrombo* syndrom*.mp.	postthrombo* syndrom*	postthrombo* syndrom*
8	post thrombo* syndrom*	post-thrombo* syndrom*.mp.	post-thrombo* syndrom*.mp.	post-thrombo* syndrom*	post-thrombo* syndrom*
9	posttrombo* syndrom*	posttrombo* syndrom*.mp.	posttrombo* syndrom*.mp.	posttrombo* syndrom*	posttrombo* syndrom*
10	post trombo* syndrom*	post-trombo* syndrom*.mp.	post-trombo* syndrom*.mp.	post-trombo* syndrom*	post-trombo* syndrom*
11	postphlebiti* syndrom*	postphlebiti* syndrom*.mp.	postphlebiti* syndrom*.mp.	postphlebiti* syndrom*	postphlebiti* syndrom*
12	post phlebiti* syndrom*	post-phlebiti* syndrom*.mp.	post-phlebiti* syndrom*.mp.	post-phlebiti* syndrom*	post-phlebiti* syndrom*
13	venous thrombosis[mh]	exp venous thrombosis/	exp postthrombosis syndrome/	[mh "venous thrombosis"]	MeSH DESCRIPTOR venous thrombosis EXPLODE ALL TREES
14	venous thromboembolism[mh]	exp venous thromboembolism/	exp vein thrombosis/	[mh "venous thromboembolism"]	MeSH DESCRIPTOR venous thromboembolism EXPLODE ALL TREES
15	postthrombotic syndrome[mh]	exp postthrombotic syndrome/	compression stocking*.mp.	[mh "postthrombotic syndrome"]	MeSH DESCRIPTOR postthrombotic syndrome EXPLODE ALL TREES
16	compression stocking*	compression stocking*.mp.	compression therap*.mp.	compression stocking*	compression stocking*
17	compression therap*	compression therap*.mp.	ECS.mp.	compression therap*	compression therap*
18	ECS	ECS.mp.	elastic stocking*.mp.	ECS	ECS
19	elastic stocking*	elastic stocking*.mp.	compression garment*.mp.	elastic stocking*	elastic stocking*
20	compression garment*	compression garment*.mp.	exp compression stocking/	compression garment*	compression garment*
21	stockings, compression[mh]	exp stockings, compression/	exp compression therapy/	[mh "stockings, compression"]	MeSH DESCRIPTOR stockings, compression EXPLODE ALL TREES
22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	or/1-15	or/1-14	{OR #1-#15}	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
23	#16 OR #17 OR #18 OR #19 OR #20 OR #21	or/16-21	or/15-21	{OR #16-#21}	#16 OR #17 OR #18 OR #19 OR #20 OR #21
24	#22 AND #23	and/22-23	and/22-23	{AND #22-#23}	#22 AND #23
25			limit 24 to exclude medline journals		

Appendix Table 2 Risk of Bias Assessment

Study, Year (Reference)	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment: Postthrombotic Syndrome	Blinding of Outcome Assessment: All-Cause Mortality	Blinding of Outcome Assessment: Venous Thromboembolism Recurrence	Blinding of Outcome Assessment: Pain in Acute Phase After Deep Vein Thrombosis	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Risk of Bias Assessment
Aschwanden et al, 2008[27]	🟢	🟢	🔴‡	🔴‡	🟢**	🔴‡	N/A	🟢††	🟢	🟢	🔴
Belcaro et al, 1993[28]	🟡*	🟡*	🔴‡	N/A	🟡*	🔴‡	N/A	🔴‖	🔴¶	🟡¶	🔴
Brandjes et al, 1997[20]	🟢	🟡†	🔴‡	🔴‡	🟢**	🔴‡	N/A	🟢††	🟢	🟢	🔴
Ginsberg et al, 2001[5]	🟢‡‡	🟢‡‡	🟢	🟢	🟢**	N/A	N/A	🟢‡‡	🟢	🟢	🟢
Jayaraj & Meissner, 2015[29]	🟡*	🟢	🔴‡	🟡§	N/A	N/A	N/A	🔴§§	🟡‖‖	🟢	🔴
Kahn et al, 2014[8]	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢††	🟢	🟢	🟢
Prandoni et al, 2004[12]	🟢	🟡†	🔴‡	🟡§	🟢**	🔴‡	N/A	🟢††	🟢	🟢	🔴

Risk of bias assessment, Cochrane Risk of Bias Tool. Red dot indicates high risk of bias; yellow, unclear risk of bias; and green, low risk of bias.

*Not explicitly reported.

†Block randomization with fixed-size blocks may have jeopardized allocation concealment, because unblinded designs may make it possible to predict subsequent allocations toward the end of each block if previous allocations are known; this may in turn introduce selection bias.[30-33]

‡Due to lack of blinding.

§Effectiveness of blinded assessment unsure, patients or stocking marks could inform assessor, although patients did not use stockings on assessment day.

‖Authors report there was attrition, but not on the reasons or size of it.

¶Due to overall lack of reporting on study design and conduct.

**Not likely to be biased by lack of blinding.

††Robust results across imputed case analyses under plausible assumptions about event rates for missing participants.

‡‡Not explicitly stated in published report. We contacted the lead author, who stated that a computerized system was used for randomization and allocation concealment, and that there was no loss to follow-up.

§§Total number of events not stated in the published report, imputed case analyses were not feasible. The authors state that the large loss to follow-up was a problem in their study. We tried to retrieve these data but could not reach the authors.

‖‖‖Number of deaths not reported.

Appendix Table 3 Excluded Studies

	Citation	Exclusion Reason
1	Elastic compression stockings reduce the incidence of postthrombotic syndrome in people with proximal deep vein thrombosis. *Evidence-Based Healthcare and Public Health*. 2005;9:81-82.	A commentary/article summary.
2	Barroy JP, Barthel J, Munck D, Goldstein M. Effect of "anti-thrombosis" stockings on the venous hemodynamics of the lower extremities. Study using mercury gauge plethysmography. *Phlebologie*. 1987;40(1):59-67 [in French].	Wrong outcomes.
3	Becker F. Post-thrombotic venous disease of the legs. Current data. *J Mal Vasc*. 1992;17(Suppl B):77-83 [in French].	Not a primary study.
4	Becker F, Menassa M, Meyer P, Brenot R, David M. Post-thrombotic venous disease of lower limbs. *Sang Thrombose Vaisseaux*. 1993;5:169-176 [in French].	Not a primary study.
5	Bernardi E, Bagatella P, Frulla M, Simioni P, Prandoni P. Postthrombotic syndrome: incidence, prevention, and management. *Semin Vasc Med*. 2001;1:71-80.	Not a primary study.
6	Bernardi E, Prandoni P. The post-thrombotic syndrome. *Curr Opin Pulm Med*. 2000;6:335-342.	Not a primary study.
7	Blattler W, Partsch H. Leg compression and ambulation is better than bed rest for the treatment of acute deep venous thrombosis. *Int Angiol*. 2003;22:393-400.	Wrong outcomes.
8	Botella FG, Gomez ML, Reparaz OP, Gadea LI. Treatment of iliofemoral deep vein thrombosis and post-thrombotic syndrome. *Angiologia*. 2013;65:218-227 [in Spanish].	Not a primary study.
9	Bouman A, Cate-Hoek AT. Timing and duration of compression therapy after deep vein thrombosis. *Phlebology*. 2014;29(1 suppl):78-82.	Not a primary study.
10	Brandjes DPM, Rutten G, Heijboer H, et al. Elastic compression stockings in the prevention of the post thrombotic syndrome in patients with a proximal deep vein thrombosis; an interim analysis. *Thromb Haemost*. 1989;1989:130.	Only interim analysis.
11	Bruhn HD. Thrombosis therapy with compression stockings. *Dtsch Med Wochenschr*. 1999;124(12):371-372 [in German].	Not a primary study.
12	Figueiredo M. Scientific evidence of compression treatment. *Jornal Vascular Brasileiro*. 2009;8:100-102 [in Portuguese].	Not a primary study.
13	Franzeck UK, Schalch I, Bollinger A. On the relationship between changes in the deep veins evaluated by duplex sonography and the postthrombotic syndrome 12 years after deep vein thrombosis. *Thromb Haemost*. 1997;77:1109-1112.	Observational study.

Appendix Table 3 Continued

	Citation	Exclusion Reason
14	Franzeck UK, Schalch I, Jager KA, Grimm ES, Bollinger A. Prospective 12-year follow-up study of clinical and hemodynamic sequelae of deep venous thromboses in patients with low risk (Zurich Study). *Wien Med Wochenschr*. 1999;149:78-84 [in German].	Observational study.
15	Franzeck UK, Schalch I, Jager KA, Schneider E, Grimm J, Bollinger A. Prospective 12-year follow-up study of clinical and hemodynamic sequelae after deep vein thrombosis in low-risk patients (Zurich study). *Circulation*. 1996;93:74-79.	Wrong study design.
16	Galanaud JP, Righini M, Quere I. Compression stockings to prevent post-thrombotic syndrome. *Lancet*. 2014;384(9938):129.	Not a primary study.
17	Garcia D. ACP Journal Club. After a first proximal DVT, compression stockings did not prevent the postthrombotic syndrome. *Ann Intern Med*. 2014;160(8):JC7.	A commentary/article summary.
18	Garcia DA. Below-knee elastic compression stockings reduced development of the postthrombotic syndrome in proximal deep venous thrombosis. *ACP J Club*. 2005;142(1):7.	A commentary/article summary.
19	Ginsberg JS, Brill-Edwards P, Kowalchuk G, Hirsh J. Intermittent compression units for the postphlebitic syndrome. A pilot study. *Arch Intern Med*. 1989;149:1651-2.	Wrong intervention
20	Ginsberg JS, Magier D, Mackinnon B, Gent M, Hirsh J. Intermittent compression units for severe post-phlebitic syndrome: a randomized crossover study. *CMAJ*. 1999;160:1303-1306.	Wrong intervention.
21	Gonzalez-Fajardo JA, Martin-Pedrosa M, Mengibar Fuente L, Salvador Calvo R, Almaraz A, Vaquero C. Quality of life after deep venous thrombosis. *Angiologia*. 2010;62:140-145 [in Spanish].	Observational study.
22	Guarnera G, Abeni D, Antignani PL, et al. Update on distal deep venous thrombosis. Reports of a multicenter study. *Int Angiol*. 2014;33(6):560-564. PubMed PMID: 24945915.	Observational study.
23	Hach-Wunderle V, Bauersachs R, Gerlach HE, et al. Post-thrombotic syndrome 3 years after deep venous thrombosis in the thrombosis and pulmonary embolism in out-patients (TULIPA) PLUS registry. *JVS: Venous and Lymphatic Disorders*. 2013;1:5-12.	Observational study.
24	Hafner J, Mayer D, Amann B, et al. Chronic venous insufficiency in postthrombotic syndrome and varicose veins. *Praxis (Bern 1994)*. 2010;99(20):1195-202 [in German].	Not a primary study.
25	Holmes CE, Bambace NM, Lewis P, Callas P, Cushman M. Effectiveness of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome (pts): a randomized control trial [Abstract No. 1087]. *Blood*. 2010;116.	Wrong comparator.

Appendix Table 3 Continued

	Citation	Exclusion Reason
26	Holmes CE, Bambace NM, Lewis P, Callas P W, Cushman M. Efficacy of a short course of complex lymphedema therapy or graduated compression stocking therapy in the treatment of post-thrombotic syndrome. *Vasc Med*. 2014;19:42-48.	Wrong comparator.
27	Ippolito E, Belcaro G, Dugall M, et al. Venoruton®: post thrombotic syndrome. Clinical improvement in venous insufficiency (signs and symptoms) with Venoruton®. A five-year, open-registry, efficacy study. *Panminerva Med*. 2011;53(3 suppl 1):13-19.	Wrong intervention.
28	Kahn SR, Azoulay L, Hirsch A, Haber M, Strulovitch C, Shrier I. Effect of graduated elastic compression stockings on leg symptoms and signs during exercise in patients with deep venous thrombosis: a randomized cross-over trial. *J Thromb Haemost*. 2003;1:494-499.	Wrong outcomes.
29	Kahn SR, Shapiro S, Houweling AH, Ducruet T, Wells PS, Rodger MA. The effectiveness of 30-40 mm HG compression stockings to treat acute leg pain associated with proximal deep vein thrombosis: Results from the SOX randomized controlled trial. *55th Annual Meeting of the American Society of Hematology*. 2013:21.	Wrong outcomes.
30	Kahn SR, Shbaklo H, Shapiro S, et al. Effectiveness of compression stockings to prevent the post-thrombotic syndrome (the SOX Trial and Bio-SOX biomarker substudy): a randomized controlled trial. *BMC Cardiovasc Disord*. 2007;7:21.	Is a study protocol.
31	Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383(9920):880-888.	Duplicate.
32	Kayssi A, Roche-Nagle G. Postthrombotic syndrome. *CMAJ*. 2014;186:62.	Not a primary study.
33	Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). [Erratum appears in *Chest*. 2008 Oct;134(4):892]. *Chest*. 2008;133:454S-545S.	Not a primary study.
34	Korstanje MJ, Neumann HA. [Compression therapy using elastic stockings]. *Ned Tijdschr Geneeskd*. 1990;134:799-802.	A commentary/article summary.
35	Korting HC. Compression stockings: No relevant conclusion from the study. *Deutsche Apotheker Zeitung*. 2009;149:84 [in German].	A commentary/article summary.
36	Labas P, Ohradka B, Vladimir J, Cambal M. The home treatment of deep vein thrombosis with low molecular weight heparin, forced mobilisation and compression. *Int Angiol*. 2000;19:303-307.	Wrong study design.

Appendix Table 3 Continued

	Citation	Exclusion Reason
37	Labropoulos N, Gasparis AP, Caprini JA, Partsch H. Compression stockings to prevent post-thrombotic syndrome. *Lancet*. 2014;384(9938):129-130.	Not a primary study.
38	Lane B, Jones S. Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. Elastic compression stockings and the risk of post-thrombotic syndrome in patients with symptomatic proximal vein thrombosis. *J Accid Emerg Med*. 2000;17:405-406.	Not a primary study.
39	Lattimer CR, Azzam M, Kalodiki E, Makris GC, Geroulakos G. Compression stockings significantly improve hemodynamic performance in post-thrombotic syndrome irrespective of class or length. *J Vasc Surg*. 2013;58:158-165.	Uses surrogate outcomes (radiographical findings).
40	Leyhe A. Is compression therapy of acute deep vein thrombosis of the leg always indicated for promoting venous flow (a basic measure)? *Internist (Berl)*. 1993;34:188-189 [in German].	Not a primary study.
41	Lofferer O, Mostbeck A, Partsch H. Compression treatment in venous and lymphatic flow disorders of the leg. *Acta Med Austriaca*. 1976;3:138-142 [in German].	Not a primary study.
42	Manganaro A, Buda D, Ando G, Consolo F. Compression therapy in deep venous thrombosis. *Minerva Cardioangiol*. 2000;48(12 suppl):57-60 [in Italian].	Not a primary study.
43	Manus JM. Venous compression therapy and thromboembolism. *Rev Infirm*. 2003;(92):29-32 [in French].	Not a primary study.
44	Markun S. Are compression stockings after deep venous thrombosis pointless? *Praxis (Bern 1994)*. 2014;103(7):409-410 [in German].	A commentary/article summary.
45	Meissner MH, Eklof B, Smith PC, et al. Secondary chronic venous disorders. *J Vasc Surg*. 2007;46(suppl S):68S-83S.	Not a primary study.
46	Milne AA, Ruckley CV. The clinical course of patients following extensive deep venous thrombosis. *Eur J Vasc Surg*. 1994;8:56-59.	Wrong study design.
47	Munteanu I. Current treatment of venous thromboembolism. *Pneumologia*. 2013;62:37-42 [in Romanian].	Not a primary study.
48	Nicolaides A, Hull RD, Fareed J. Prevention of postthrombotic syndrome. *Clin Appl Thromb Hemost*. 2013;19:213-215.	Not a primary study.
49	O'Donnell MJ, McRae S, Kahn SR, et al. Evaluation of a venous-return assist device to treat severe post-thrombotic syndrome (VENOPTS). A randomized controlled trial. *Thromb Haemost*. 2008;99:623-629.	Wrong intervention.
50	Partsch H. Ambulation and compression after deep vein thrombosis: dispelling myths. *Semin Vasc Surg*. 2005;18:148-152.	Not a primary study.

Appendix Table 3 Continued

	Citation	Exclusion Reason
51	Partsch H. Experimental proofs of compression method effectiveness. *Angeiologie*. 2009;61:55-56 [in French].	Not a primary study.
52	Partsch H. The Role of Leg Compression in the Treatment of Deep Vein Thrombosis. *Phlebology*. 2014;29:66-70.	A commentary/article summary.
53	Partsch H, Blattler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. *J Vasc Surg*. 2000;32:861-869.	Wrong outcomes.
54	Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. *Int Angiol*. 2004;23:206-212.	Wrong intervention.
55	Partsch H, Mosti G. Thigh compression. *Phlebology*. 2008;23:252-258.	Not a primary study.
56	Pavkov M. Prevention of postthrombotic disease. *Angeiologie*. 2000;52:88-89 [in French].	Not a primary study.
57	Perri S, Amendolara M, Gallo G, et al. Ambulatory treatment of postphlebitic ulcers of lower limbs. Physiopathological bases and clinical results. *G Chir*. 1994;15(8-9):371-380 [in Italian].	Wrong study design.
58	Prandoni P. Elastic stockings, hydroxyethylrutosides or both for the treatment of post-thrombotic syndrome. *Thromb Haemost*. 2005;93:183-185.	Wrong comparator.
59	Prandoni P, Noventa F, Quintavalla R, et al. Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. *Blood*. 2012;119:1561-1565.	Wrong comparator.
60	Prandoni P, Villalta S, Bagatella P, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica*. 1997;82:423-428.	Wrong study design.
61	Rabe E. Thigh-length versus lower leg compression stockings for the prevention of postthrombotic syndrome in patients with proximal deep leg vein thrombosis: A randomized study. *Vasomed*. 2013;25:57 [in German].	A commentary/article summary.
62	Rabe E, Hertel S, Bock E, Hoffmann B, Jockel K H, Pannier F. Therapy with compression stockings in Germany — results from the Bonn Vein Studies. *J Dtsch Dermatol Ges*. 2013;11:257-262.	Observational study.
63	Rocca A, Compagna R, Vito D, Della Corte GA, Bianco T, Amato B. Compression therapy in chronic venous disease. European Surgical Research Conference: 24th National Congress of the Italian Society of Young Surgeon, SPIGC 2011 Naples Italy Conference Start: 20111013 Conference End: 20111016 Conference Publication: (varpagings). 2012;49:140.	A commentary/article summary.

Appendix Table 3 Continued

	Citation	Exclusion Reason
64	Roumen-Klappe EM, den Heijer M, van Rossum J, et al. Multilayer compression bandaging in the acute phase of deep-vein thrombosis has no effect on the development of the post-thrombotic syndrome. *J Thromb Thrombolysis*. 2009;27:400-405.	Wrong intervention.
65	Rutten G, Brandjes DPM, Huisman M, et al. The effect of a size to fit graded compression stocking on the development of the post thrombotic syndrome (PTS) in patients with a proximal deep vein thrombosis, measured with a clinical score: an interim analysis. *Br J Haematol*. 1990;76:19.	Only interim analysis.
66	Saedon M, Stansby G. Post-thrombotic syndrome: prevention is better than cure. *Phlebology*. 2010;25(Suppl 1):14-19.	Not a primary study.
67	Steins A, Jünger M. Value of compression therapy in treatment of deep venous thrombosis. *Wien Med Wochenschr*. 1999;149:54-55; discussion 6 [in German].	Not a primary study.
68	Stoberl C. [Compression therapy in post-thrombotic syndrome]. *Wien Med Wochenschr*. 1994;144:233-237 [in German].	Not a primary study.
69	Stucker M, Link K, Reich-Schupke S. Compression therapy in vein diseases without intervention: Chronic vein insufficiency, deep vein thrombosis, postthrombotic syndrome and leg ulcer. *Vasomed*. 2014;26:90-95 [in German].	A commentary/article summary.
70	Ten Cate-Hoek AJ. How long should compression therapy be carried out after deep venous thrombosis?. *Vasomed*. 2012;24:30-31 [in German].	Not a primary study.
71	ten Cate-Hoek A J. Elastic compression stockings—is there any benefit? *Lancet*. 2014;383:851-853.	A commentary/article summary.
72	Ten Cate-Hoek AJ, Ten Cate H, Tordoir J, Hamulyak K, Prins MH. Individually tailored duration of elastic compression therapy in relation to incidence of the postthrombotic syndrome. *J Vasc Surg*. 2010;52:132-138.	Wrong study design.
73	Ten Cate-Hoek AJ, Ten Cate H, Tordoir J, Hamulyak K, Prins MH. Individually tailored duration of compression stockings therapy in relation to the incidence of postthrombotic syndrome. *Vasomed*. 2010;22:125-126 [in German].	A commentary/article summary.
74	Ten Cate-Hoek AJ, Ten Cate H, Tordoir J, Hamulyak K, Prins MH. Individually tailored duration of elastic compression therapy in relation to incidence of the postthrombotic syndrome. *Vasomed*. 2011;23:104 [in German].	A commentary/article summary.
75	Thoma K, Petter O, Bischof J, Wendekamm U. Indication-related management of peripheral venous insufficiency using compression stockings. *Z Arztl Fortbild (Jena)*. 1986;80:1029-1032 [in German].	Not a primary study.

Appendix Table 3 Continued

	Citation	Exclusion Reason
76	van der Velden S, Neumann H. The post-thrombotic syndrome and compression therapy. *Phlebology*. 2014;29:83-89.	Not a primary study.
77	Vazquez SR, Kahn SR. Advances in the diagnosis and management of postthrombotic syndrome. *Best Pract Res Clin Haematol*. 2012;25:391-402.	Not a primary study.
78	Vicaretti M. Compression therapy for venous disease. *Australian Prescriber*. 2010;33:186-190.	Not a primary study.
79	Vowden P, Vowden K. How should compression hosiery be used for patients who have had deep venous thrombosis? *Wounds UK*. 2007;3:89.	A commentary/article summary.
80	Wentel TD, Neumann H A. Management of the postthrombotic syndrome: the Rotterdam approach. *Semin Thromb Hemost*. 2006;32:814-821.	Not a primary study.
81	White R, Brown A, Lattimer CR, Geroulakos G, Elstone A. Compression therapy post-deep vein thrombosis: how to best avoid post-thrombotic syndrome. *Wounds UK*. 2013;9:8-14.	A commentary/article summary.
82	Whittaker L, Baglin T, Vuylsteke A. Challenging the evidence for graduated compression stockings. *BMJ*. 2013;346:f3653.	Not a primary study.
83	Wilhelmsson S, Ulfvengren M, Hammaren A. Compression therapy after acute venous thrombosis of the leg. Good results with a teamwork model. *Lakartidningen*. 1985;82:2601-2602 [in Swedish].	Not using randomization or quasi-randomized method for group allocation.
84	Willeke A, Lindhoff-Last E. Treatment of venous thromboembolism. *Internist (Berl)*. 2010;51:335-336, 338 [in German].	Not a primary study.