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Full Length Article

Compression stockings to prevent post-thrombotic syndrome in adults, a Bayesian meta-analysis☆

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ABSTRACT

Background: Prescription of compression stockings to prevent post-thrombotic syndrome (PTS) in adults is controversial. We sought to estimate the efficacy of compression stockings vs. placebo/no intervention (control) in preventing PTS, and to estimate the probability of observing a benefit when prescribing compression stockings to prevent PTS.

Methods: We conducted a systematic review of the literature in MEDLINE, EMBASE, and the Cochrane Central Register of Randomized Trials, searching for randomized controlled trials that compared compression stockings, applied in the acute setting of deep vein thrombosis, vs. control to prevent PTS. We used a Bayesian approach for data analysis.

Results: Four studies met our inclusion criteria. When comparing intervention vs. control, the estimated odds ratio (OR) was 0.57 (95% Credible Interval (CrI): 0.21 to 1.20) for PTS vs. no PTS and 0.79 (95% CrI 0.31 to 1.67) for severe vs. no/mild/moderate PTS. The probabilities of observing treatment benefits in the population if prescribing compression stockings ranged between 47% (large benefit, OR < 0.50) and 95% (small benefit, OR < 1.00) for any PTS and between 16% and 82% (from large to small benefit) for severe PTS. The probabilities of observing benefit of compression stockings in a future study ranged 44%–76% and 25%–72% (from large to small benefit) for any PTS and severe PTS, respectively.

Conclusion: Despite heterogeneity, data show that it is still probable to observe some degree of treatment benefit when prescribing compression stockings and to observe some degree of treatment benefit in a future study.

1. Background

Post-thrombotic syndrome (PTS) is a long-term complication that affects 20–50% of adults who sustain deep vein thrombosis (DVT) [1]. Established PTS can lead to significant disability and poor health-related quality of life [1]. The negative effect of PTS is largely due to the limited options to treat this syndrome. For this reason, PTS prevention is considered paramount and hence, the focus of several research efforts.

Until recently, graduated elastic compression stockings were prescribed to prevent PTS in adults at risk [2]. Supporting their use, a pooled analysis of randomized controlled trials (RCT) conducted between the 1990s and the early 2000s [3–7] concluded that compression stockings reduced the incidence of PTS by 50% [8]. Despite their heterogeneity (e.g., type and pressure of the stockings, time to intervention, length of follow up), the studies showed a lower absolute frequency of PTS in patients assigned to the stockings garment arm. For > 10 years these studies, which randomized over 600 patients, provided the rationale for the recommendation of prescribing compression stockings to prevent PTS as an evidence-based option [2,9]. However, the efficacy of stockings for PTS prevention was challenged in 2014 with the publication of the SOX trial [10]. The trial, which enrolled 806 patients, showed compression stockings to have no effect. The efficacy of compression stockings to prevent PTS in adults has remained controversial since then. In fact, at least seven meta-analyses of RCTs have been published in the years following the SOX trial [11–17]. All these studies highlight the heterogeneity of the individual trials, the possible benefit of compression stockings to prevent PTS in some subgroups of patients, and the overall uncertainty of the estimates.

The present work aimed to analyze the existing data from a

☆ All authors had access to the data and a role in writing the manuscript.

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Table 1
Search strategy.

Database	Search term	Number of citations
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) < 1946 to March 5, 2019 >	1 postthrombotic syndrome/	637
	2 Postphlebitic Syndrome/	627
	3 (postthrombo* or postphlebit* or post thrombo* or post phlebit*).tw,kf.	3498
	4 1 or 2 or 3	3845
	5 exp. Bandages/	23,583
	6 (bandage* or stocking* or sock* or compress* or elastic* or legging* or hose* or hosiery*).tw,kf.	236,027
	7 5 or 6	253,964
	8 4 and 7	694
	9 randomized controlled trial.pt.	477,053
	10 controlled clinical trial.pt.	92,943
	11 randomized.ab.	436,184
	12 placebo.ab.	195,825
	13 randomly.ab.	306,559
	14 trial.ab.	455,680
	15 groups.ab.	1,886,844
	16 9 or 10 or 11 or 12 or 13 or 14 or 15	2,724,263
	17 8 and 16	165
Embase Classic + Embase < 1947 to 2019 Week 09 >	1 postthrombosis syndrome/	2838
	2 (postthrombo* or postphlebit* or post thrombo* or post phlebit*).tw,kw.	5735
	3 1 or 2	6439
	4 exp. “bandages and dressings”/	49,643
	5 (bandage* or stocking* or sock* or compress* or elastic* or legging* or hose* or hosiery*).tw,kw.	306,217
	6 4 or 5	346,155
	7 3 and 6	1296
	8 random:.tw. or clinical trial:.mp. or exp. health care quality/	4,818,804
	9 7 and 8	543
Database: EBM Reviews - Cochrane Central Register of Controlled Trials < February 2019 >	1 postthrombotic syndrome/	79
	2 Postphlebitic Syndrome/	61
	3 (postthrombo* or postphlebit* or post thrombo* or post phlebit*).tw,kf.	313
	4 1 or 2 or 3	348
	5 exp. Bandages/	2577
	6 (bandage* or stocking* or sock* or compress* or elastic* or legging* or hose* or hosiery*).tw,kf.	10,803
	7 5 or 6	12,492
	8 4 and 7	123

Bayesian perspective. The Bayesian framework offers key advantages over classical meta-analysis, including a more natural interpretation of results in terms of probabilities, the ability to estimate the probability of a particular range of results, and flexibility to allow incorporation of uncertainty in its parameters [18,19].

We sought to estimate the odds of PTS in adult patients at risk when comparing compression stockings (intervention) vs. placebo or no intervention. In addition, we aimed to estimate the probability of observing large and small treatment benefits with the prescription of compression stockings in the population as well as in a hypothetical future study. This information could be used by the clinician to inform patients as to the probability of decreasing their risk of PTS to different degrees in order for the patients to make an informed decision regarding their willingness to use of compression stockings.

2. Methods

2.1. Eligibility criteria

We included RCTs that compared the efficacy of applying compression stockings vs. placebo or no intervention during acute DVT, defined as ≤1 month after DVT diagnosis, to prevent PTS in adult patients.

In view of the known heterogeneity of the existing studies, we focused on the efficacy of compression stockings applied during the acute phase of DVT (≤1 month). The importance in the timing of application of a preventive measure in PTS has been highlighted in more recent studies [9,20].

2.2. Search strategies

A comprehensive literature search using the OVID search platform was conducted with the help of a research librarian. The searches included MEDLINE (1946–March 5, 2019), EMBASE (1947–Week 9, 2019), and the Cochrane Central Register of Randomized Trials; the terms used in the search are shown in Table 1. No language or publication year restrictions were applied. Only published articles were considered. Titles and abstracts were initially scanned by two reviewers (MM, CL), who then retrieved and assessed relevant papers for eligibility. The references of eligible studies were also screened in order to identify other potential studies that might have been missed during the search.

2.3. Data abstraction

Data on the frequency of the outcome were independently extracted from eligible studies by two members of the research team (LA, LB); disagreements were resolved through discussion. When required, authors were contacted to obtain further information.

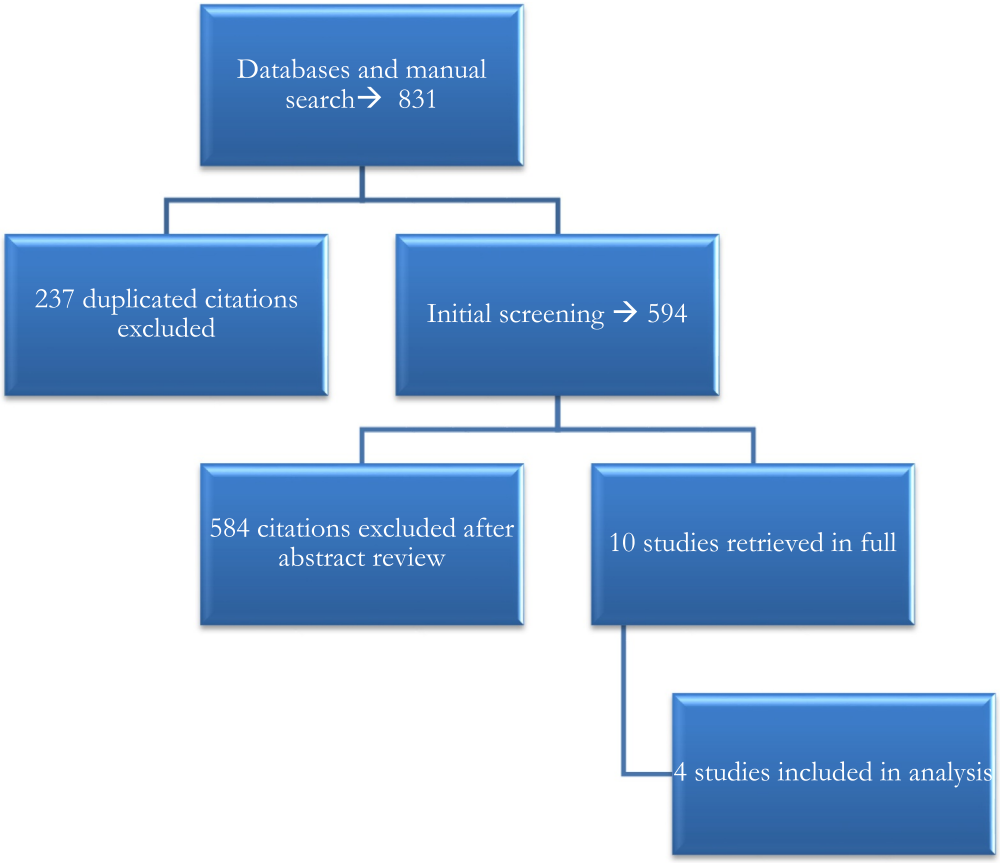

Fig. 1. Flow chart showing study selection process.

2.4. Risk of bias assessment

The methodology of the included studies was evaluated with the Cochrane Collaboration tool for the assessment of risk of bias [18].

2.5. Summary measures and data synthesis

We first estimated the odds ratio (OR) for treatment effect considering two outcome categorizations: 1) PTS of any severity vs. no PTS and 2) severe PTS vs. no/mild/moderate PTS. Time-unadjusted and time-adjusted analyses were carried out, in order to take into account the differences of follow-up times in the studies. Second, we estimated the probability of observing benefit prescribing compression stockings 1) in the population and 2) in a hypothetical future study, at different thresholds ranging from an OR of < 1.0 (corresponding to any benefit), through values of < 0.5 (corresponding to a large benefit) in decreases of 0.1.

Random effects logistic model analyses were fitted using JAGS 4.3.0 and rjags version 4.6, using three independent chains. We used an uninformative prior distribution (mean 0, standard deviation 10) for the logarithm of the population OR, so that only the data from the different trials informed the results. We used an informative log-normal prior distribution for the between-study standard deviation (sigma); this prior is the predictive distribution of the between-study standard deviation from meta-analyses of subjective outcomes and non-pharmacological interventions [21]. This approach is particularly useful in meta-analyses of a small number of trials where heterogeneity is imprecisely estimated from the data.

In addition, meta-regression was used to account for different follow-up times across trials; the average treatment effect at the average follow-up time was estimated. Convergence was assessed with the Gelman-Rubin statistic. Pooled OR are presented as the posterior mean and 95% credible interval (CrI) computed from 10,000 samples from each chain after convergence.

Whenever possible, the results of the Villalta Scale were considered in order to allow for some homogeneity in the definition of PTS. For trials that assessed the outcome across several time points, we considered the incidence of PTS at the time of the last assessment or at the time after which no additional events were reported.

3. Results

Eight hundred and forty-seven studies were identified through the literature search (Fig. 1). After excluding duplicates, 594 studies were included in the initial screening. Ten studies were retrieved in full, four of which met our inclusion criteria and were included in the analysis. Six studies were excluded due to application of the intervention outside the window of interest [5,6,22], or due to the study design, which encouraged all patients to wear the same type of compression stockings either after an initial intervention [7,23] or for a different length of time [24].

The four included studies randomized 632 patients to receiving compression stockings and 617 to placebo or no intervention. The median age of the participants was 57.6 years; 53.5% were male. The intervention consisted of knee-high compression stockings administering a pressure of 30–40 mmHg at the ankle level. The time to intervention varied from 3 to 21 days post-DVT. The time points for outcome assessment used in the analysis were 6 [25], 24 [10], 36 [3], and 37 and 52 (the latter for severe PTS) [4] months post-DVT. A shortest time point (6 months) was chosen for the first study [25] due to the high attrition observed thereafter. Only one study did not apply the Villalta scale for outcome assessment [4]. Self-reported adherence to the intervention varied from 55.6% to 87%. Three studies used no compression stockings as control [3,4,25] and one study used placebo

Table 2
Characteristics of included studies.

Study, year	Type of patient	Intervention	Comparison	Time to intervention	Treatment	Randomization	Blinding
Brandjes, 1997	First venogram proven proximal DVT (popliteal or above) irrespective of calf vein thrombosis	Knee-length stocking, 40 mmHg at ankle	No stocking	2–3 weeks after DVT	Heparin followed by warfarin	Sealed envelope, blocks of 8	NA
Prandoni, 2004	Clinically symptomatic proximal DVT	Knee-length stocking, 30–40 mmHg at ankle	No stocking	Randomized 5–10 days after admission	Unfractionated or low molecular weight heparin followed by warfarin	Computer generated randomization list, blocks of 20	NA
Kahn, 2014	First symptomatic proximal DVT (popliteal or above)	Knee-length stocking 30–40 mmHg at ankle	Stocking < 5 mmHg at the ankle	Within 2 weeks of DVT diagnosis	Unfractionated or low molecular weight heparin followed by warfarin	Web-based randomization system, stratified by center, blocks of 4 and 8	Patient, health care provider, study personnel and statistician
Jayaraj, 2015	Acute proximal DVT	Stocking 30–40 mmHg at ankle	No stocking	3 days	Unfractionated or low molecular weight heparin followed by warfarin	Sealed envelope, stratified by center, blocked randomization	NA

Study, year	Patient mean age	Proportion of males	Adjudication	PTS assessment tool	Time of assessment used	Assessment of compliance	Reported adherence	Prescribed use of stocking
Brandjes, 1997	60 years	56%	Independent investigator	Brandjes criteria	37 and 52 months	4-point scale, self-reported	76% always	During the day, at least 2 years
Prandoni, 2004	60–63 years	43%	Investigator unaware of treatment allocation	Villalta scale	36 months	Self-reported (notebook)	87% at least 80% of daytime	During the day or longer, for 2 years
Kahn, 2014	55 years	60%	Investigator unaware of treatment allocation	Villalta scale and Ginsberg's criteria	24 months	Self-reported (number of day/week, number of hours/day)	56% at least 3 days/week at 24 months	From waking to retiring, for 2 years
Jayaraj, 2015	48 years	51%	Investigator unaware of treatment allocation	Villalta scale and Venous Clinical Severity Score	6 months	Self-reported, compliance calendar + interviews	60% at two years	–

Fig. 2. Summary of risk of bias assessment.

stockings that applied < 5 mmHg of pressure at the ankle level [10]. Compression stockings were prescribed for two years or more after DVT diagnosis. Characteristics of individual studies can be seen in Table 2.

Results of the risk of bias assessment are shown in Fig. 2. The lack of blinding of the participants in three of the trials [3,4,25] may have introduced bias when patients reported PTS symptoms to the outcome assessors (performance bias), and has been highlighted by experts in the field. In addition, allocation concealment was not explained in sufficient detail to confidently exclude risk of bias in these three manuscripts.

Although the SOX trial met the criteria for low risk of bias in all risk of bias categories, it must be pointed out that some issues, such as the low frequency of adherence to the intervention and the possible preventive effect of the small amount of pressure provided by the placebo stockings, have been highlighted as problematic by experts in the field [16,26,27].

Gelman diagnostics and plots suggested convergence of the Bayesian models. The time-unadjusted pooled OR for intervention vs. placebo or no intervention was 0.57 (95% CrI: 0.21 to 1.20) for the outcome PTS vs. no PTS and 0.79 (95% CrI 0.31 to 1.67) for the outcome severe PTS vs. no/mild/moderate PTS. Forest plots for each outcome are shown in Fig. 3.

For meta-regression analysis, study-specific and pooled OR for PTS were estimated at 26 months for any PTS and 30 months for severe PTS, which was the average observed follow-up time across studies for each comparison. The time-adjusted estimated OR was 0.59 (95% CrI 0.28–1.01) for the outcome PTS vs. no PTS and 0.94 (95% CrI 0.41–1.81) for the outcome severe PTS vs. no/mild/moderate PTS.

The predicted OR in a new study was estimated at 0.95 (95% CrI

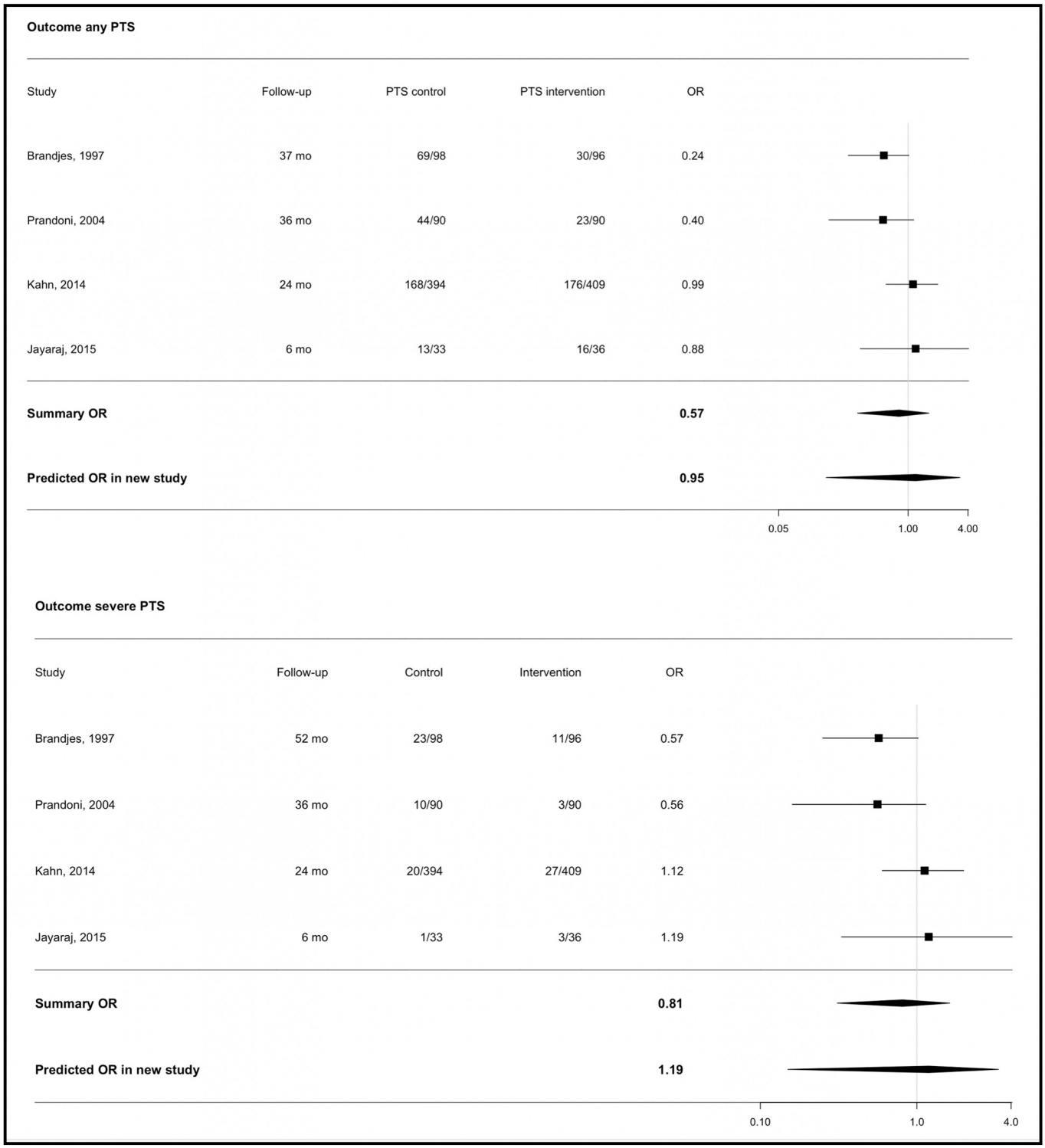

Fig. 3. Odds ratios and 95% credible intervals for the outcomes any post-thrombotic syndrome and severe post-thrombotic syndrome.
Legend: PTS refers to post-thrombotic syndrome, OR to odds ratio.

0.08–3.26) for any PTS vs. no PTS and 1.19 (95% CrI 0.15–3.32) for severe PTS vs. no/mild/moderate PTS. The probabilities of observing treatment benefit in the population if prescribing compression stockings and for a hypothetical future study are shown in Table 3. For example, the mean probability of an OR < 0.50 in the population, which is similar to the results of the pre-SOX trials, was estimated at 47.3% for any PTS and 15.7% for severe PTS. Similarly, there is a 43.5% probability that the OR for a future study would be < 0.50 in favor of compression stockings for any PTS and 25.2% for severe PTS.

4. Discussion

The Bayesian ORs for treatment effect found herein are in line with the results of some of the recent frequentist meta-analyses [11,13,15], and show that it is probable to observe a protective effect of compression stockings when applied in the acute setting of a DVT. This

Table 3
Probability of the outcome given a range of odds ratios for compression stockings vs. control.

Threshold OR	Probability of population OR lying below the threshold (%)		Probability of OR for future study lying below the threshold (%)	
	Any PTS: OR 0.57 (CrI: 0.21–1.20)	Severe PTS: OR 0.79 (CrI: 0.31–1.67)	Any PTS: OR 0.95 (CrI: 0.08–3.26)	Severe PTS: OR 1.19 (CrI: 0.15–3.32)
0.50	47.3	15.7	43.5	25.2
0.60	66.9	29.4	53.2	35.5
0.70	80.1	45.7	61.0	46.4
0.80	88.0	61.4	67.2	57.0
0.90	92.4	73.5	72.2	65.3
1.00	95.0	82.0	76.0	72.1

Legend: OR refers to odds ratio.; PTS, to post-thrombotic syndrome; CrI, to Credible interval

effect is more evident for having vs. not having PTS than for severe PTS vs. no/mild/moderate PTS.

The pathophysiology of PTS may depend on the relation between the inflammatory response observed in the context of DVT and thrombus resolution. The potentially evolving nature of inflammation response after a DVT may explain the fact that compression stockings show probability of benefit when applied in the acute setting [9].

The Bayesian approach used for data analysis allowed us to estimate the probability that compression stockings, on average, would reduce the risk of PTS, as well as the probability that compression stockings would reduce the risk of PTS in a future study, an important distinction in the presence of study-to-study heterogeneity.

Overall, our results suggest that there is still a large probability (95%) that, on average, compression stockings prevent PTS of any severity. Although the 95% CrI for the ORs include 1, this should not be interpreted as meaning that there is no benefit (just as a p-value > 0.05 does not mean 'no benefit').

The Bayesian approach quantifies the evidence for benefit in a way that may make it easier for the clinician to inform the patient about the probability of decreasing their risk of PTS to different degrees. For example, patients can be informed that there is 95% probability of observing some reduction in the risk of PTS of any severity and 72% probability of observing some reduction in the risk of severe PTS. By contrast, large benefits are unlikely: the probability of reducing the odds of any PTS by half is around 50%, and the probability of reducing the odds of severe PTS by half is around 15%. The information can be weighed against the cost and overall burden implied in using the stockings, in order for the patients to make an informed decision as to their willingness to use the stockings to reduce their risk of PTS to a level they find acceptable.

We also estimated the probability of observing a benefit in a hypothetical future study. This is relevant, since one of the most important goals of meta-analysis is the future application of gained knowledge [19]. In fact, an advantage of the Bayesian approach over a classical statistical analysis is that it allows the estimation of a predictive distribution for the true effect in a future trial providing results that can be intuitively interpreted, such as the probability that the effect would exceed a given specified level [19]. The probability that a future study will show some effect of compression stockings to prevent PTS is around 76% for any PTS and 72% for severe PTS. This information could be used to decide whether including compression stockings in future trials investigating other potential strategies to prevent PTS is warranted.

Of note, two new trials were published after the SOX trial; these two studies, the IDEAL DVT [24] and OCTAVIA [22], investigated whether individualized or shorter length of compression stocking wear was effective for PTS prevention. The trials were not included in the present analysis since they did not meet our inclusion criteria in terms of comparing compression stockings to no compression or placebo.

It must be pointed out that we evaluated the outcomes at the last time point after which no new events were recorded. This is particularly relevant for two of the trials for which the overall follow-up time was longer than the time after which no new events were registered, which could mistakenly lead one to interpret that longer follow up was associated with higher probability of seeing a beneficial effect of compression stockings.

There are limitations to the present study. The trials included are heterogeneous in several aspects, including the variability in the time to intervention and to outcome assessment, and how PTS was defined. We limited the first two factors by only including studies that applied compression stockings during the first month post-DVT, though even a month might be too long in the setting of the inflammatory response that ensues a thrombotic event [9], and by exploring the effect of time through the use of meta-regression. We also considered the outcome assessment as per the Villalta Scale, when available. Moreover, one of the strengths of our study is the use of a Bayesian approach for analyzing the data, which is more appropriate than frequentist analysis in view of the small number of included trials and their heterogeneity. Indeed, differences between trials are known to arise for a number of reasons, including their particular study design, methodological issues, and random variation [19]. When trial results are combined in a meta-analysis and between-study heterogeneity is expected, random effects models are generally considered appropriate to estimate the main effect as well as between-study variance [19,21]. However, meta-analyses that include a small number of trials can lead to an imprecise estimation of between-study heterogeneity when the analysis is performed using conventional random effects models [28,29]. In this situation, a Bayesian approach allows researchers to incorporate external evidence for estimating the extent of between-study heterogeneity, resulting in more robust estimations of the main effect [21]. The heterogeneity among studies is reflected in the relatively wide credible intervals predicted for the effect of compression stockings in a future study reported herein and shown in Fig. 3. Importantly, there is no explicit weighting in the Bayesian meta-analysis. Data from each study are entered directly into a model and the relative contribution of that study to the pooled estimate is determined largely by the concentration around the point estimate of the likelihood for that study. A small study or one with few events will have a likelihood that is very flat, and it will contribute less to the overall estimate than a large study with a likelihood focused around the point estimate.

In sum, the Bayesian perspective shows that the prescription of a non-invasive measure such as compression stockings appears to still play a role in PTS prevention. The different probabilities of PTS for a series of OR shown herein could be used for shared decision-making when deciding whether to prescribe compression stockings. Lastly, it is still possible that a new trial will show benefit of compression stockings for PTS prevention.

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Author contribution

Study design: Laura Avila, Leonardo Brandao. Literature search: Alana Marson. Study screening, risk of bias assessment: Madeline Montoya, Celeste Lumia, Laura Avila, Leonardo Brandao. Data extraction: Laura Avila, Leonardo Brandao. Data analysis, interpretation of

results: Laura Avila, George Tomlinson. Manuscript writing: Laura Avila. Critically reviewed the manuscript: Leonardo Brandao, Madeline Montoya, Celeste Lumia, Alana Marson, George Tomlinson.

Declaration of competing interest

The authors declare no potential conflict of interest.

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