

Do we need a second “SOX” trial to evaluate  
the role of stockings in the prevention of  
PTS?

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# Introduction

- Lower limb pain, oedema, skin discolouration or ulceration occur in upto 50% of patients post DVT
- PTS is the clinical manifestation of sustained ambulatory venous hypertension from deep venous scarring, valve incompetence or both
- Economic losses occur from nursing time for bandages and loss of working days for patients

# Current standard of care

Grade 1A evidence



**NICE** National Institute for  
Health and Care Excellence

## Venous thromboemboli diseases

Evidence Update April 2014

A summary of selected new evidence relevant to NICE clinical guideline 144 'Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing' (2012)

**Evidence Update 55**

### Mechanical interventions

Routine long-term use of graduated elastic compression stockings does not appear to prevent post-thrombotic syndrome in patients with a first proximal DVT.

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AMERICAN COLLEGE OF  
 **CHEST**  
P H Y S I C I A N S\*

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- **Routine use of compression stockings is out to prevent postthrombotic syndrome in acute DVT.** Based on recent evidence, the 10th edition suggests *not* to routinely use compression stockings to prevent postthrombotic syndrome in patients with acute DVT. Postthrombotic syndrome is a chronic condition of the leg with swelling, pain, skin discoloration, and even ulcers. In the 9th edition, compression stockings were routinely suggested as a preventive measure in these patients.

# Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

Clinical guideline

Published: 27 June 2012

[nice.org.uk/guidance/cg144](http://nice.org.uk/guidance/cg144)

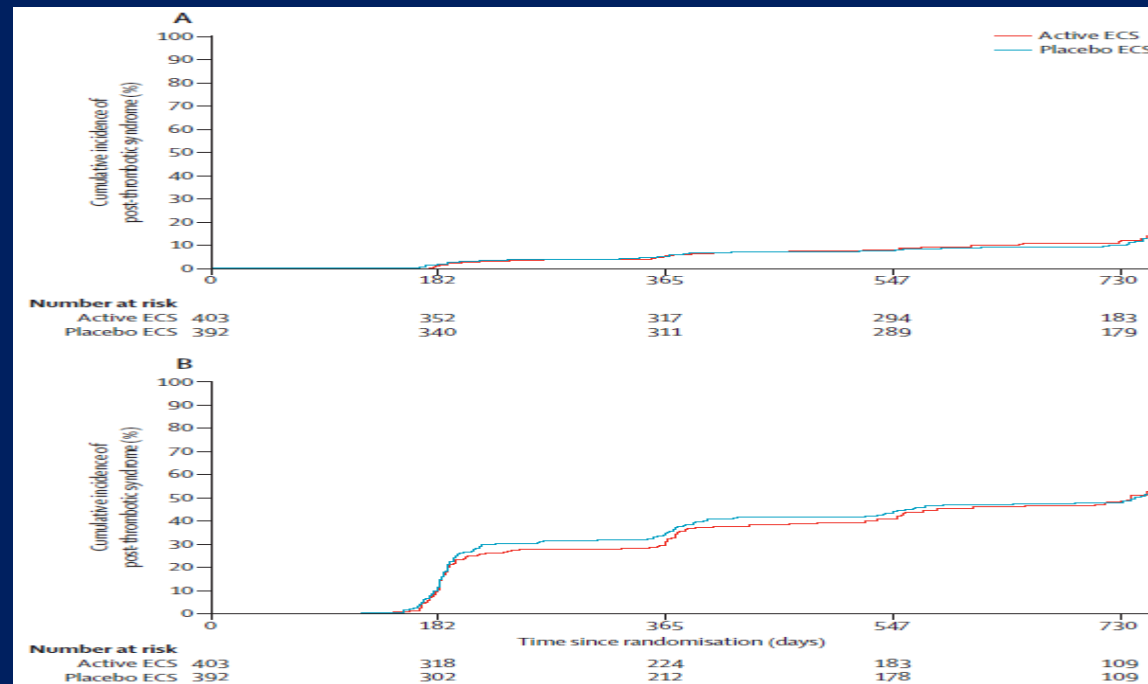
## Mechanical interventions

### *Proximal deep vein thrombosis or pulmonary embolism*

- 1.2.9 Do not offer elastic graduated compression stockings to prevent post-thrombotic syndrome or VTE recurrence after a proximal DVT. This recommendation does not cover the use of elastic stockings for the management of leg symptoms after DVT. [new 2015]

# Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

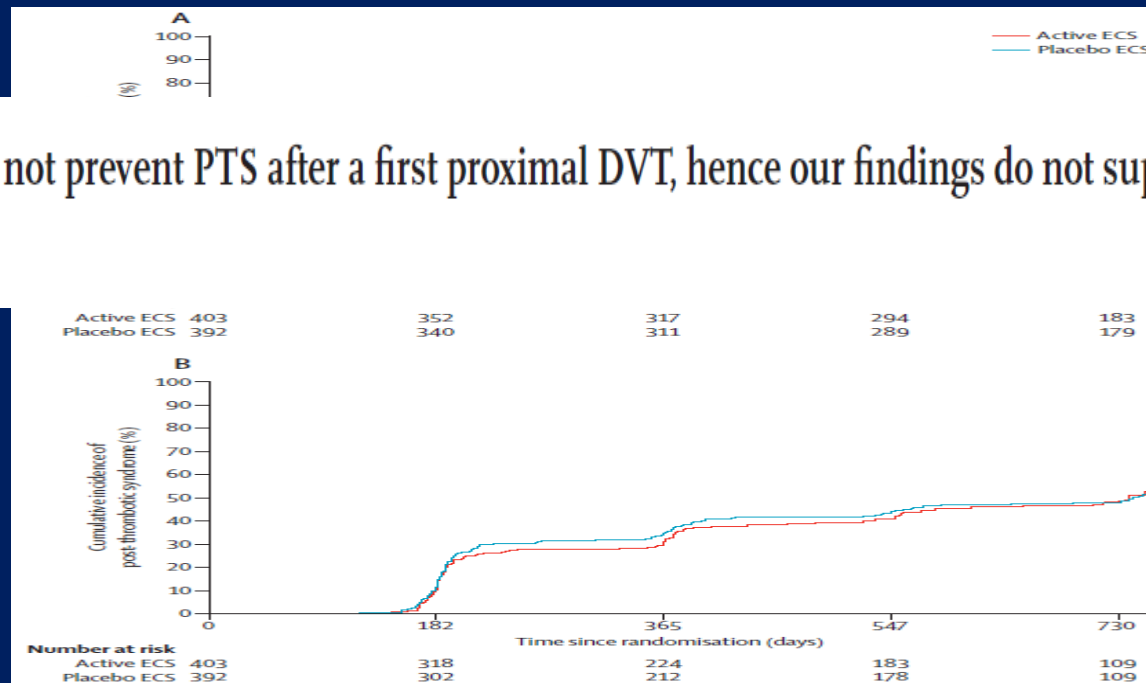
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# Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

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**Interpretation** ECS did not prevent PTS after a first proximal DVT, hence our findings do not support routine wearing of ECS after DVT.





# Systematic Review and Meta-Analysis of Utility of Graduated Compression Stockings in Prevention of Post-Thrombotic Syndrome

A.L. Skervin <sup>a</sup>, A. Thapar <sup>a</sup>, A.J. Franchini <sup>b</sup>, P. Prandoni <sup>c</sup>, J. Shalhoub <sup>a</sup>, A.H. Davies <sup>a,\*</sup>

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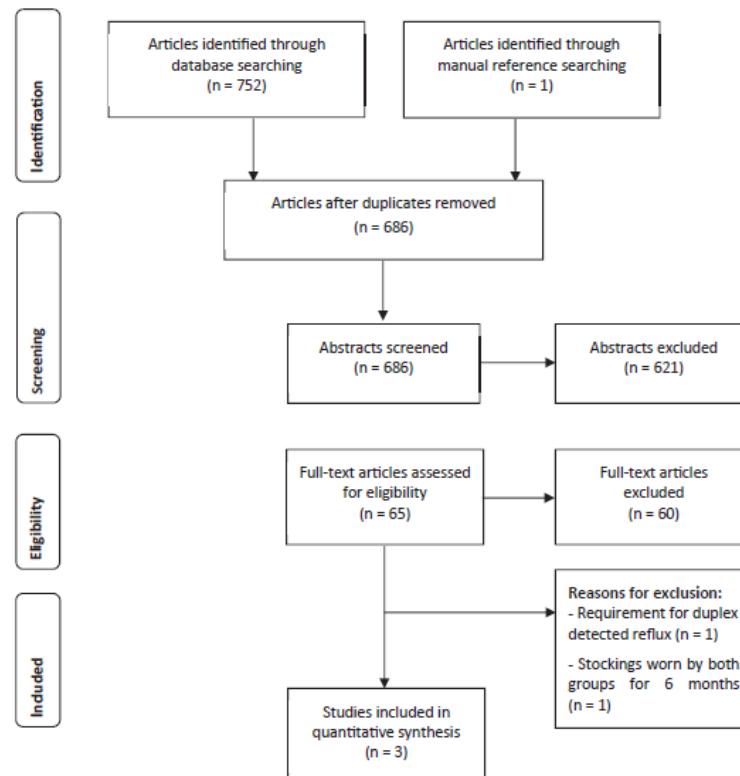
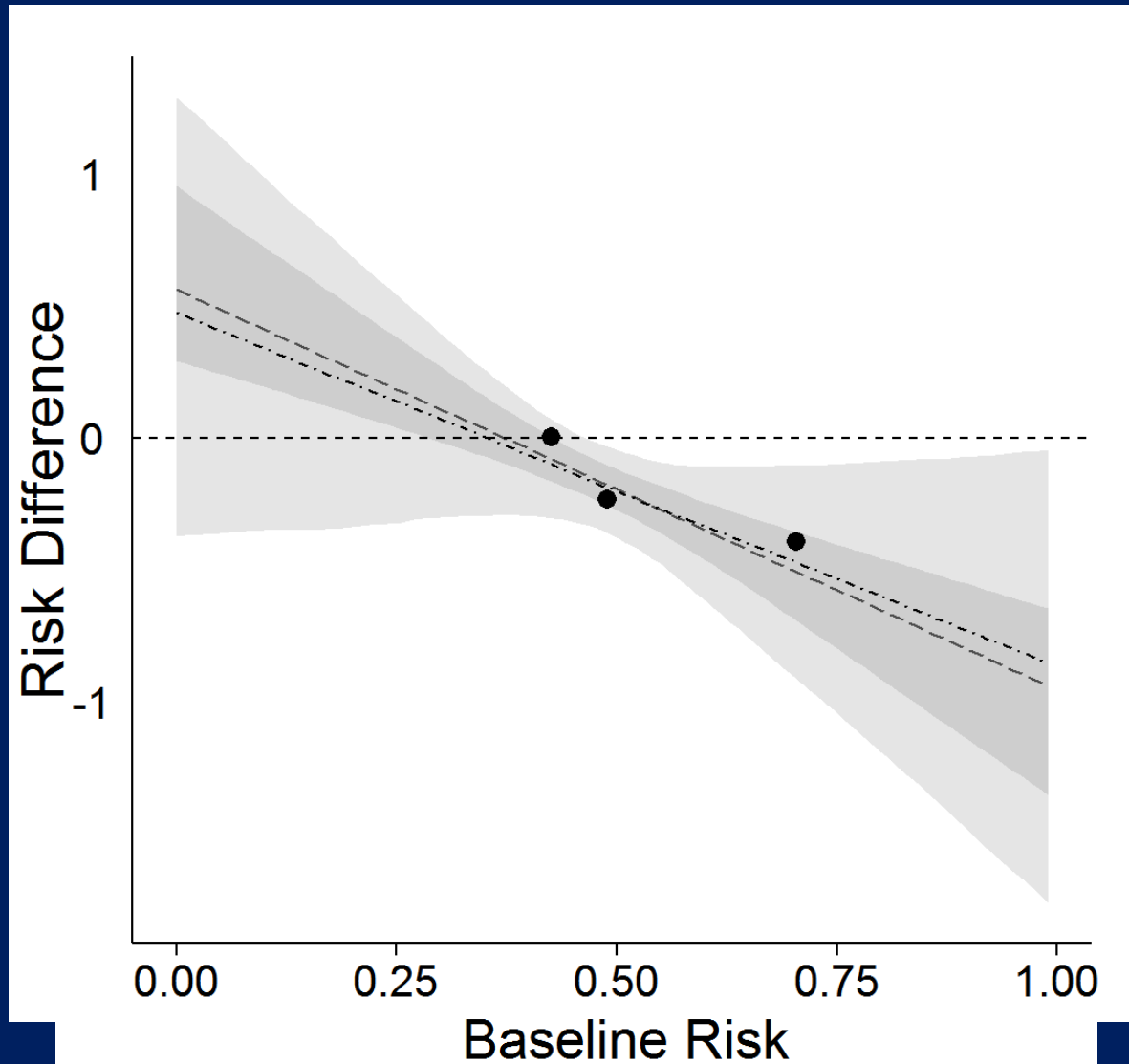


Figure 1. PRISMA diagram.

# Risk of bias

|               | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---------------|---|---|---|---|--|--------------------------------------|------------|
| Brandjes 1997 | +   | -                                       | -   | +   | -  | +                                    | +          |
| Khan 2014     | +   | +                                       | +   | +   | +  | +                                    | +          |
| Prandoni 2004 | +   | +                                       | -   | +   | +  | +                                    | -          |

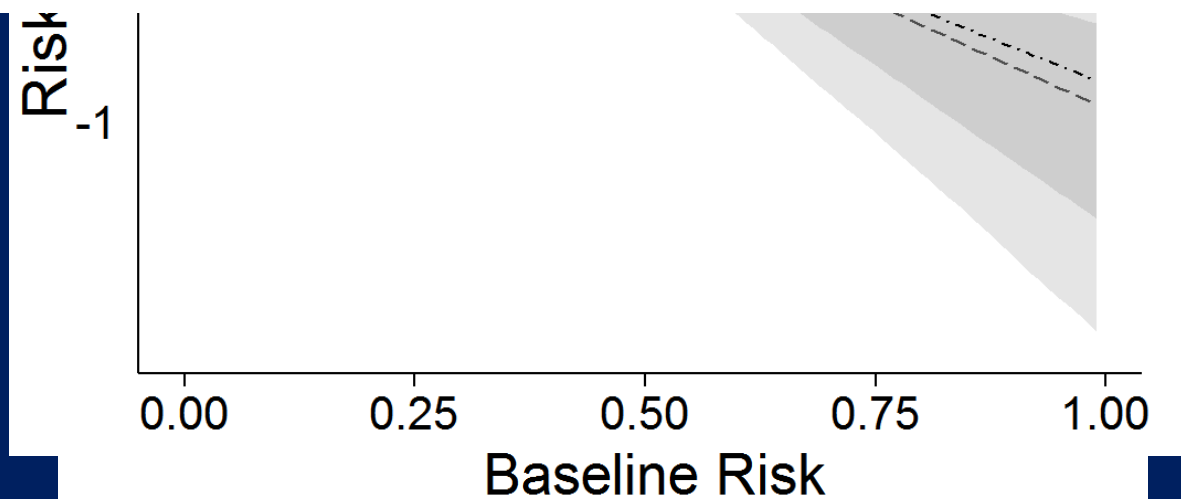
# Higher baseline risk of PTS and increased benefit of GCS?



# Higher baseline risk of PTS and increased benefit of GCS?



**Results:** A total of 686 articles were screened. Three randomised controlled trials inclusive of 1,177 patients were eligible for inclusion. PTS developed in 49–70% of control patients at 5 years. High statistical heterogeneity was observed between trials (all PTS:  $I^2 = 0.94$ ; severe PTS:  $I^2 = 0.79$ ). The risk difference in PTS incidence between control and GCS arms varied from 0% to 39% between trials. In trials with a higher baseline prevalence of PTS, a visual trend towards more benefit with GCS was noted.



## CONCLUSION

Current data are too heterogeneous to conclude whether a real treatment effect for GCS exists. The trials studied indicate that approximately half of patients develop PTS in the first 2 years post DVT. If tolerated, the effect of GCS may be limited to symptom relief from the acute DVT.<sup>28</sup> More evidence is needed to aid clinicians to deliver reliable recommendations for the use of GCS in preventing PTS.

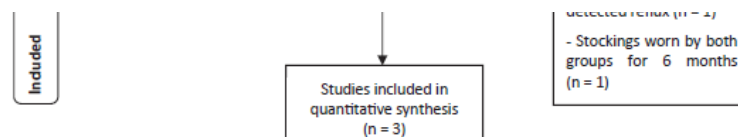


Figure 1. PRISMA diagram.

REVIEW

## Systematic Review and Meta-Analysis of Utility of Graduated Compression Stockings in Prevention of Post-Thrombotic Syndrome

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### WHAT THIS PAPER ADDS

Post-thrombotic syndrome (PTS) is a chronic debilitating sequelae of deep vein thrombosis (DVT), affecting up to 50% of patients. There are three high-quality randomised trials from which to infer evidence on the use of compression stockings in the prevention of PTS. A systematic review and meta-analysis of these trials revealed significant clinical, methodological, and statistical heterogeneity and no consistency of effect. The role of compression stockings following DVT remains uncertain, with further evidence needed. Consensus on their efficacy in preventing PTS would either reduce patient morbidity, or the inconvenience and healthcare costs associated with compression stockings.

# Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials

*Rajeeve Subbiah, Vikas Aggarwal, Huaqing Zhao, Raghu Kolluri, Saurav Chatterjee, Riyaz Bashir*

*Lancet Haematol 2016*

Published Online

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# Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials

Rajeev Subbiah, Vikas Ag

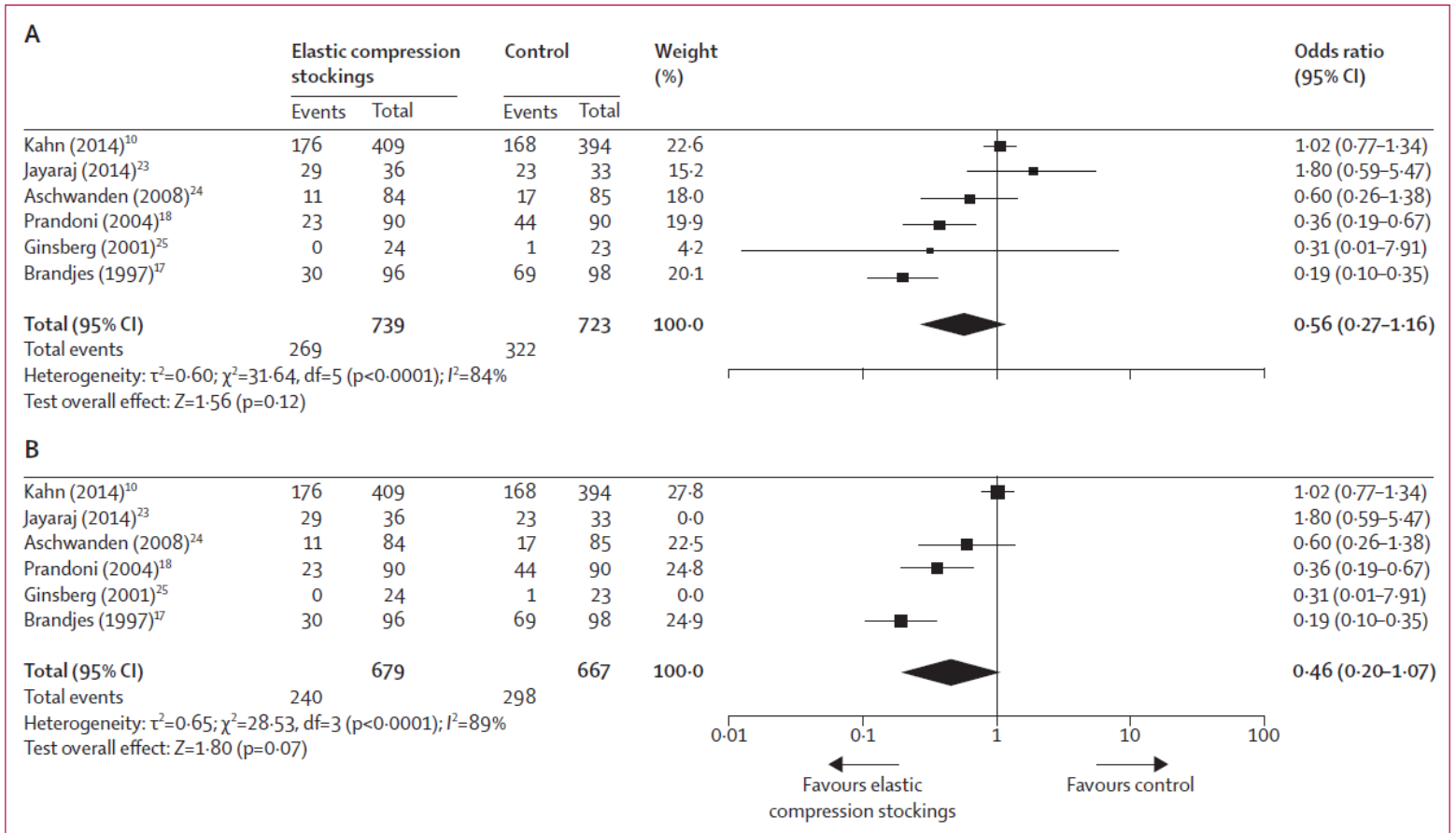


Figure 2: Effect of elastic compression stockings in patients with deep vein thrombosis on post thrombotic syndrome (A) and sensitivity analysis of highest quality only studies (B; defined as >100 patients, >70% follow-up, adequate randomisation, post thrombotic syndrome primary endpoint; excludes Jayaraj and colleagues<sup>23</sup> and Ginsberg and colleagues<sup>24</sup>)



# Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials

Rajeeve Subbiah, Vikas Ag

A

|                                 | Elastic compression stockings |       | Control |       | Weight (%) |  | Odds ratio (95% CI) |
|---------------------------------|-------------------------------|-------|---------|-------|------------|--|---------------------|
|                                 | Events                        | Total | Events  | Total |            |  |                     |
| Kahn (2014) <sup>10</sup>       | 176                           | 409   | 168     | 394   | 22.6       |  | 1.02 (0.77-1.34)    |
| Jayaraj (2014) <sup>23</sup>    | 29                            | 36    | 23      | 33    | 15.2       |  | 1.80 (0.59-5.47)    |
| Aschwanden (2008) <sup>24</sup> | 11                            | 84    | 17      | 85    | 18.0       |  | 0.60 (0.26-1.38)    |
| Prandoni (2004) <sup>18</sup>   | 23                            | 90    | 44      | 90    | 19.9       |  | 0.36 (0.19-0.67)    |
| Ginsberg (2001) <sup>25</sup>   | 0                             | 24    | 1       | 23    | 4.2        |  | 0.31 (0.01-7.91)    |

## Implications of all the available evidence

In view of this equipoise shown in our study, we would suggest that at this time there does not exist sufficient data to show that use of compression therapy is not beneficial. Our study shows need for continued conduct of randomised controlled trials addressing this issue in a more pragmatic fashion.

quality only studies (B; defined as >100 patients, >70% follow-up, adequate randomisation, post thrombotic syndrome primary endpoint; excludes Jayaraj and colleagues<sup>23</sup> and Ginsberg and colleagues<sup>24</sup>)

# Does prescription of medical compression prevent development of post-thrombotic syndrome after proximal deep venous thrombosis?

Michel Perrin<sup>1</sup> and Bo Eklöf<sup>2</sup>

Phlebology

2016, Vol. 31(3) 160–169

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**Results:** We identified five randomized controlled trials (RCTs) before the SOX trial including 798 patients with acute proximal deep vein thrombosis.

- Brandjes (1997): at two years' follow-up, elastic compression stockings reduced post-thrombotic syndrome by 50%;
- Ginsberg (2001): no difference in post-thrombotic syndrome with or without elastic compression stockings after more than two years' follow-up;
- Partsch (2004): elastic compression stockings with routine above knee and early ambulation reduced the incidence and severity of post-thrombotic syndrome after two years' follow-up;
- Prandoni (2004) showed significantly less post-thrombotic syndrome after elastic compression stockings for two years with a five-year follow-up;
- Aschwanden (2008) showed no difference with elastic compression stockings after three years' follow-up.

# Does prescription of medical compression prevent development of post-thrombotic syndrome after proximal deep venous thrombosis?

Michel Perrin<sup>1</sup> and Bo Eklöf<sup>2</sup>

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**Conclusion:** Prescription of elastic compression stockings for the prevention of post-thrombotic syndrome is now in doubt. Immediate compression after diagnosis of acute deep vein thrombosis to prevent swelling and reduce pain, permitting early ambulation in combination with adequate anticoagulation has proven benefit, although a secondary analysis of the SOX trial refutes this belief. Continued long-term compression treatment is questioned. Two major questions remain:

- Is the lack of positive outcome on the development of post-thrombotic syndrome after proximal deep vein thrombosis due to the fact that there were a few patients with iliofemoral extension in the quoted randomized controlled trials who may benefit from prolonged medical compression treatment?
- Compliance is the major issue, and the two randomized controlled trials with excellent control of compliance showed significant reduction in the rate of post-thrombotic syndrome, but we know that in daily practice the adherence is closer to Kahn's data.

# Graduated compression stockings to treat acute leg pain associated with proximal DVT

## A randomised controlled trial

Susan R. Kahn<sup>1</sup>; Stan Shapiro<sup>1,2</sup>; Thierry Ducruet<sup>1</sup>; Philip S. Wells<sup>3</sup>; Marc A. Rodger<sup>3,4</sup>; Michael J. Kovacs<sup>5</sup>; David Anderson<sup>6,7</sup>; Vicky Tagalakis<sup>1</sup>; David R. Morrison<sup>1</sup>; Susan Solymoss<sup>8</sup>; Marie-José Miron<sup>9</sup>; Erik Yeo<sup>10</sup>; Reginald Smith<sup>11</sup>; Sam Schulman<sup>12,13</sup>; Jeannine Kassis<sup>14</sup>; Clive Kearon<sup>12</sup>; Isabelle Chagnon<sup>15</sup>; Turnly Wong<sup>16</sup>; Christine Demers<sup>17</sup>; Rajendar Hanmiah<sup>18</sup>; Scott Kaatz<sup>19</sup>; Rita Selby<sup>20</sup>; Suman Rathbun<sup>21</sup>; Sylvie Desmarais<sup>22</sup>; Lucie Opatrny<sup>23</sup>; Thomas L. Ortel<sup>24</sup>; Jean-Philippe Galanaud<sup>25</sup>; Jeffrey S. Ginsberg<sup>12</sup>

| Visit    | Mean (SD)*          |                      | Difference in means<br>(95% CI) | P-value |
|----------|---------------------|----------------------|---------------------------------|---------|
|          | Active ECS<br>N=409 | Placebo ECS<br>N=394 |                                 |         |
| Baseline | 5.18 (3.29)<br>409  | 5.38 (3.29)<br>393   | 0.20 (-0.26, 0.66)              | 0.39    |
| 14-day   | 2.39 (2.59)<br>392  | 2.47 (2.61)<br>385   | 0.08 (-0.29, 0.45)              | 0.67    |
| 1-month  | 1.88 (2.67)<br>386  | 1.70 (2.33)<br>377   | -0.18 (-0.53, 0.18)             | 0.33    |
| 60-day   | 1.39 (2.19)<br>377  | 1.13 (1.86)<br>365   | -0.27 (-0.56, 0.03)             | 0.08    |

\* mean (standard deviation) numerical pain rating score, based on a scale of 10 (0, no pain; 10, worst possible pain).

## What does this paper add?

- We performed a large, placebo controlled multicentre randomised trial of active versus placebo compression stockings in patients with proximal DVT.
- We found that active stockings did not reduce leg pain, compared with placebo stockings, at any of the time points measured (14 days, 30 days and 60 days after DVT).
- Results were similar for frequent stockings users and by categories of age, sex and extent of DVT.
- Thus, elastic compression stockings do not appear to reduce leg pain in patients with acute proximal DVT.

# Venous thromboembolic diseases: diagnosis, management and thrombophilia testing

Clinical guideline

Published: 27 June 2012

[nice.org.uk/guidance/cg144](http://nice.org.uk/guidance/cg144)

## *8 Stockings for preventing post-thrombotic syndrome in patients with DVT*

What is the effectiveness of stockings, when adherence is adequate, for preventing post-thrombotic syndrome in people with confirmed deep vein thrombosis?

### **Why is this important?**

While there have been trials of elastic graduated compression stockings for preventing PTS following proximal DVT, there are aspects of these studies that make it difficult to be certain about the outcomes. In addition, these studies have differed considerably on whether or not the use of these stockings is effective. The Committee noted the importance of ensuring adherence in research on any possible preventative role of elastic compression stockings.

The Committee concluded that the currently available research evidence does not aid decision-making, due to the uncertainty of the output. [new 2015]

## Discussion

No consistent effect of GCS was noted

Trials were methodologically and statistically very different

The lower compliance and lower baseline risk of PTS in SOX may partly account for the lack of benefit for GCS

A large trial is needed to confirm or refute the findings of SOX