

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Thigh length versus knee length anti-embolism stockings for the prevention of deep vein thrombosis in postoperative surgical patients; a systematic review and network meta-analysis
AUTHORS	Wade, Ros; Paton, Fiona; Rice, Stephen; Stansby, Gerard; Millner, Peter; Flavell, Hayley; Fox, Dave; Woolacott, Nerys F.

VERSION 1 - REVIEW

REVIEWER	Martin Dennis University of Edinburgh UK I was chief investigator of the CLOTS trials in stroke. Covidien provide their TEDS and SCD devices to our trial centres
REVIEW RETURNED	31-Jul-2015

GENERAL COMMENTS	<p>This is a well designed and clearly written systematic review of the evidence concerning the relative effectiveness of thigh and knee length GCS in surgical patients. However, I do think this needs to be interpreted in the context of the wider literature concerning GCS, and DVT prophylaxis (see suggestions for discussion).</p> <p>On p 26 the authors state that “and knee length stockings with heparin were statistically significantly more effective than heparin alone (median OR 0.68, 95% CrI: 0.27 to 1.38).” – but the 95% CI include OR = 1? Is this a typo? These figures suggest that adding knee length GCS does not add to heparin</p> <p>The following points might be alluded to in the discussion</p> <p>Although the authors identify that the marginal benefits of thigh-length stockings plus heparin vs heparin alone, and smaller than those of heparin vs no heparin on DVT, this has to be taken in clinical context where heparin causes bleeding which may worsen important outcomes (like survival), where stockings tend to cause less significant adverse effects e.g. skin problems.</p> <p>This review does attempt to come to some conclusion about how stockings might be used in surgical practice – i.e. use thigh length whether they can be used, and use knee length in all others. However, if one takes a slightly different approach to the interpretation of the evidence one arrives at rather different conclusions.</p> <p>I would conclude from trials of thigh-length GCS vs no stockings in surgery that they reduce the risk of DVT in surgery patients alone, or in addition to heparin.</p> <p>Looking at the trials of knee length stockings vs no stockings, with or</p>
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	<p>without heparin, I would conclude that they are few in number but there is no reliable evidence that they have any effect on DVT rate – certainly no statistically significant effect, and there are very wide CIs around the effect.</p> <p>The trials comparing the two lengths directly tend to favour the thigh length GCS but the trials have been too small to demonstrate superiority of thigh length stockings, or equivalence of knee length</p> <p>On this basis we do not know that below knee stockings have any effect on DVT risk after surgery, so why subject patients to them and why spend huge amounts of public money on them. Certainly when we looked in Scotland, 75% of all GCS purchased by the NHS were knee length. Is it really the case that only 25% of patients can use thigh length stockings effectively, or does providing knee length stockings give clinicians the excuse to provide an easier, but probably ineffective intervention?</p> <p>Our CLOTS 2 trial (n= 3114) suggested that there was a statistically significant difference in the DVT rate between immobile stroke patients treated with thigh and knee length GCS. Whilst this evidence comes from a different patient group the result was based on 236 proximal DVTs. Our CLOTS trial 1 (thigh-length DVT vs None) had shown that thigh length GCS did not reduce the risk of DVT, so that putting the two trials together might even suggest that below knee DVT increase the risk of DVT. I wonder whether your discussion should include discussion of whether evidence from other patient groups should help inform decision making.</p> <p>Also, although the conclusions refer to the use of GCS in surgical patients it only mentions their use in combination with heparin – the evidence supporting the use of intermittent pneumatic compression vs None is stronger for that relating to GCS. I think this needs to be mentioned – see meta analyses below</p> <p>The CLOTS Trials Collaboration. Thigh-length versus below-knee stockings for DVT prophylaxis after stroke: a randomized trial. <i>Ann Int Med</i> 2010;153:553–562.</p> <p>Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, et al; CLOTS Trials Collaboration. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. <i>Lancet</i>. 2009;373:1958-65. [PMID: 19477503]</p> <p>Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, et al. Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis. <i>Health Technol Assess</i>. 2005;9:iii-iv, ix-x, 1-78. [PMID: 16336844]</p> <p>Ho KM, Tan JA. Stratified Meta-Analysis of Intermittent Pneumatic Compression of the Lower Limbs to Prevent Venous Thromboembolism in Hospitalized Patients Circulation. 2013;128:1003-1020.</p>
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REVIEWER	Mr MS Sajid
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	Western Sussex Hospitals NHS Trust, Worthing Hospital Worthing, West Sussex BN14 8BA United Kingdom
REVIEW RETURNED	08-Aug-2015

GENERAL COMMENTS	Very nicely written article and should be published. My only concern is that previously published Cochrane review showed similar outcome and recommendations. This article did not anything new in current literature apart from the addition of pool meta-analysis. Authors did not compared their results with conclusion of previously published Cochrane review and failed to justify this study. In ideal situation I would like to see this issue added in the discussion section when authors must justify their study before publication
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REVIEWER	Smitaa Patel University of Birmingham UK
REVIEW RETURNED	22-Oct-2015

GENERAL COMMENTS	<ol style="list-style-type: none"> 1. The research question is clearly defined and easy to understand 2. The abstract is clear and concise and is a good summary of the review 3. Study design is not applicable here as this is a systematic review 4. In the search strategy section the authors clearly describe what databases they have searched for their articles. The systematic review databases were searched up to August 2013 and trial databases January 2010 to February 2014, I wondered why there was a difference in dates searched for both types of databases? Also the search terms used have not been described so if I was to repeat the search I couldn't. 5. Research ethics are not required but the review has a PROSPERO registration number. 6. Authors have described DVT to be the outcome they are looking at 7. Analysis methods are appropriately described and used 8. Some of the studies included in the study are quite old which the authors mention in the limitations 9. The results address the research question. Perhaps some p-values should be presented with the results so it can be seen if the results are significant or not 10. Some of the results are in text only and are quite hard to read and digest. They maybe better in a forest plot or table and maybe presenting p-values too would make them easy to quickly read and understand. For example the sub-group analysis of orthopaedic surgery versus non-orthopaedic surgery 11. The discussion and conclusions are justified by the results 12. Study limitations are described 13. PRISMA and extra tables available 14. To the best of my knowledge the paper is free from concerns over publication 15. The standard of English is excellent <p>Please check: On page 10 you say "knee length stockings with heparin was statistically significantly more effective than heparin alone (median OR 0.68, 95% CrI: 0.27 to 1.38)" but the confidence implies that this result is not significant, please check</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1) On p 26 the authors state that “and knee length stockings with heparin were statistically significantly more effective than heparin alone (median OR 0.68, 95% CrI: 0.27 to 1.38).” – but the 95% CI include OR = 1? Is this a typo? These figures suggest that adding knee length GCS does not add to heparin.

Response: Apologies, this was an error in our manuscript, which we have now corrected.

2) The following points might be alluded to in the discussion

Although the authors identify that the marginal benefits of thigh-length stockings plus heparin vs heparin alone, and smaller than those of heparin vs no heparin on DVT, this has to be taken in clinical context where heparin causes bleeding which may worsen important outcomes (like survival), where stockings tend to cause less significant adverse effects e.g. skin problems.

Response: Our systematic review aimed to compare the clinical effectiveness of knee length versus thigh length stockings for the prevention of DVT in surgical patients. As part of that assessment, we undertook a network meta-analysis which included a comparison of all relevant treatments (including pharmacological prophylaxis) for the outcome DVT. It was not the aim of this review to compare the adverse effects of compression stockings with those of pharmacological prophylaxis. However, as part of the review we did identify some limited data on adverse events; only twelve of the 23 trials reported results relating to adverse events, including minor bleeding complications associated with pharmacoprophylaxis, although the proportion of patients reporting such events was low; between 1% and 4%. This additional information on adverse events of pharmacoprophylaxis has been added to the results section. We have stated in the discussion section that evidence relating to other outcomes was sparse, including adverse events.

3) This review does attempt to come to some conclusion about how stockings might be used in surgical practice – i.e. use thigh length whether they can be used, and use knee length in all others. However, if one takes a slightly different approach to the interpretation of the evidence one arrives at rather different conclusions.

I would conclude from trials of thigh-length GCS vs no stockings in surgery that they reduce the risk of DVT in surgery patients alone, or in addition to heparin.

Response: Our review aimed to compare the clinical effectiveness of thigh length stockings with knee length stockings (with or without standard pharmacological prophylaxis) for the prevention of DVT in surgical patients. A Cochrane review by Sachdeva et al. (2010) has assessed whether compression stockings (either alone, or on a background of another method of prophylaxis) reduce the risk of DVT in hospitalised patients. Therefore, this question has already been addressed using systematic review methods. As part of our assessment, we undertook a network meta-analysis which included a comparison of all relevant treatments in order to utilise indirect as well as direct evidence to inform this comparison of thigh length stockings with knee length stockings (with or without standard pharmacological prophylaxis). There were 21 unique effectiveness outcomes produced from the network meta-analysis. Of these, we reported the results for which the analysis was intended and summarised the effectiveness of each treatment using the absolute risk of DVT estimates. The marginal effectiveness of thigh length stockings with pharmacological prophylaxis was reported to help interpret the effectiveness of the most effective treatment. We have clarified the interpretation of the probability of being the most effective treatment results in the text, i.e. it does not simply reflect the

effectiveness of the treatment, but also the uncertainty in the estimate.

4) Looking at the trials of knee length stockings vs no stockings, with or without heparin, I would conclude that they are few in number but there is no reliable evidence that they have any effect on DVT rate – certainly no statistically significant effect, and there are very wide CIs around the effect.

The trials comparing the two lengths directly tend to favour the thigh length GCS but the trials have been too small to demonstrate superiority of thigh length stockings, or equivalence of knee length

On this basis we do not know that below knee stockings have any effect on DVT risk after surgery, so why subject patients to them and why spend huge amounts of public money on them. Certainly when we looked in Scotland, 75% of all GCS purchased by the NHS were knee length. Is it really the case that only 25% of patients can use thigh length stockings effectively, or does providing knee length stockings give clinicians the excuse to provide an easier, but probably ineffective intervention?

Response: No trials comparing knee length stockings plus pharmacoprophylaxis versus pharmacoprophylaxis alone met the inclusion criteria for our systematic review. Two trials compared knee length stockings with no stocking, when pooled the result was not statistically significant. The two trials were old and heterogeneous; therefore, we concluded that the evidence base was weak. The results of our network meta-analysis reflect the trial evidence that there is some, but not strong, evidence that knee length stockings are more effective than no treatment, as stated in the results section.

5) Our CLOTS 2 trial (n= 3114) suggested that there was a statistically significant difference in the DVT rate between immobile stroke patients treated with thigh and knee length GCS. Whilst this evidence comes from a different patient group the result was based on 236 proximal DVTs. Our CLOTS trial 1 (thigh-length DVT vs None) had shown that thigh length GCS did not reduce the risk of DVT, so that putting the two trials together might even suggest that below knee DVT increase the risk of DVT. I wonder whether your discussion should include discussion of whether evidence from other patient groups should help inform decision making.

Also, although the conclusions refer to the use of GCS in surgical patients it only mentions their use in combination with heparin – the evidence supporting the use of intermittent pneumatic compression vs None is stronger for that relating to GCS. I think this needs to be mentioned – see meta analyses below

Response: Our systematic review aimed to compare the clinical effectiveness of knee length versus thigh length stockings for the prevention of DVT in surgical patients. We did not include any studies of other patient groups. We also did not attempt to assess other methods of mechanical prophylaxis, such as intermittent pneumatic compression. We have added a paragraph to the discussion section regarding other patient groups, specifically stroke patients and the CLOTS2 trial.

Reviewer 2:

Very nicely written article and should be published. My only concern is that previously published Cochrane review showed similar outcome and recommendations. This article did not anything new in current literature apart from the addition of pool meta-analysis. Authors did not compared their results with conclusion of previously published Cochrane review and failed to justify this study. In ideal situation I would like to see this issue added in the discussion section when authors must justify their study before publication.

Response: The previous Cochrane review that compared knee length versus thigh length anti-

embolism stockings is discussed at the beginning of the Discussion section; we compare our results with those of the previous review. The previous review included three of the five studies included in our direct meta-analysis. Our review also included a network meta-analysis, which allowed us to compare all the relevant treatments for the prevention of DVT in surgical patients and analyse the effect of incorporating indirect evidence of the relative effectiveness of thigh length stockings with knee length stockings (with or without standard pharmacological prophylaxis). The results indicated that thigh length stockings plus pharmacological prophylaxis was the most effective treatment, and that the inclusion of indirect evidence did not increase the precision of effect estimates indicating statistical heterogeneity across the trials. A further trial would need to be large to assess clinically relevant DVT across a heterogeneous population. Therefore, this study represents a more up-to-date and broader assessment of the evidence than the Cochrane review, which also contributed to a value of information analysis. In addition, we discussed the practicalities of undertaking a new trial comparing thigh length with knee length anti-embolism stockings. Any similarity in outcomes or conclusions should not determine the value of an analysis.

Reviewer 3:

1. The research question is clearly defined and easy to understand
2. The abstract is clear and concise and is a good summary of the review
3. Study design is not applicable here as this is a systematic review
4. In the search strategy section the authors clearly describe what databases they have searched for their articles. The systematic review databases were searched up to August 2013 and trial databases January 2010 to February 2014, I wondered why there was a difference in dates searched for both types of databases? Also the search terms used have not been described so if I was to repeat the search I couldn't.
5. Research ethics are not required but the review has a PROSPERO registration number.
6. Authors have described DVT to be the outcome they are looking at
7. Analysis methods are appropriately described and used
8. Some of the studies included in the study are quite old which the authors mention in the limitations
9. The results address the research question. Perhaps some p-values should be presented with the results so it can be seen if the results are significant or not
10. Some of the results are in text only and are quite hard to read and digest. They maybe better in a forest plot or table and maybe presenting p-values too would make them easy to quickly read and understand. For example the sub-group analysis of orthopaedic surgery versus non-orthopaedic surgery
11. The discussion and conclusions are justified by the results
12. Study limitations are described
13. PRISMA and extra tables available
14. To the best of my knowledge the paper is free from concerns over publication
15. The standard of English is excellent

Response: In response to point 4, we searched guideline and systematic review databases up to August 2013 (when we started the project) to identify reviews of anti-embolism stockings. We searched the included and excluded studies lists of relevant reviews to identify relevant primary studies for our review. At the protocol development stage we identified two relevant Cochrane reviews, one published in 2010, one published in 2012. Therefore, we updated our searches by searching for primary studies from January 2010 onwards, as it was anticipated that any earlier relevant primary studies would have been identified by the searches for the previous two Cochrane reviews. We have added the search terms used to the Search strategy section.

In response to point 9, we have stated for each result whether it was, or was not, statistically significant.

Please check:

On page 10 you say "knee length stockings with heparin was statistically significantly more effective than heparin alone (median OR 0.68, 95% CrI: 0.27 to 1.38)" but the confidence implies that this result is not significant, please check

Response: Apologies, this was an error in our manuscript, which we have now corrected.

VERSION 2 – REVIEW

REVIEWER	Smitaa Patel University of Birmingham
REVIEW RETURNED	10-Dec-2015

GENERAL COMMENTS	I still think it would be good to see p-values with odds ratios and confidence intervals. Forest plots are also easier to look at the results
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VERSION 2 – AUTHOR RESPONSE

We have added p-values for the results, as requested. Instead of a forest plot, we have provided a supplementary table of the full results for the no interaction model. A forest plot of results for one comparator only presents a subset of the results and doesn't cover all the results in the paper.