Author’s response to reviews

Title: Effects of preventive use of compression stockings for elderly with chronic venous insufficiency and swollen legs: A systematic review and meta-analysis

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Cover letter: Decision on Manuscript BGTC-D-18-00707

Entitled: Effects of preventive use of compression stockings for elderly with chronic venous insufficiency and swollen legs: A systematic review and meta-analysis

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Thank you for offering such a rapid peer-review process and for giving us the opportunity to re-submit a revised version of this manuscript. The peer-review comments have been helpful, and many of them have helped us improving the manuscript. We have revised the manuscript in accordance with the reviewers’ recommendations and suggestions. All authors have approved the revised manuscript.

In the following, we summarise how we have followed up on the peer-review comments. Reviewers’ comments are followed by comments from the authors, starting with a bold “A.” In the revised manuscript new and revised text are shown as track changes.
Reviewer’s number 1, C. W. Fan comments:

Title: consider using "...secondary prevention of venous ulceration with compression stockings and symptoms of chronic venous insufficiency in older person …" in the title

A: We searched for all kind of prevention (primary, secondary and tertiary), but the studies we identified were all focusing on secondary prevention. As the search and selection process was not limited to studies about secondary prevention, we think it would be misleading to put ‘secondary prevention’ into the title.

Abstract Please include the results of the symptoms of chronic venous insufficiency.

A: We have added the following sentence in the abstract: “We found no difference between class 2 and class 1 stockings on subjective symptoms of chronic venous insufficiency or outcomes of vein thrombosis or mobility were found.” (page 2, third paragraph).

The thrombosis and mobility were included in methods but there was no mentioned of the findings of thrombosis and mobility in the results Page 2, line 54

A: As stated above, we have introduced a new sentence into the result section of the abstract.

Rephrase the sentence please, either state that " patients wearing Grade 3 compression stockings had lower recurrence risk compared with patients with stockings, (RR 0.46 etc)" or "patients not wearing stockings were at higher recurrence risk than those wearing Grade 3 compression stockings (RR >1 …)

A: We have followed this suggestion and revised the sentence to: “In another study patients wearing class 3 compressions stockings had lower recurrence risk compared with patients without stockings (RR 0.46; 95% CI 0.27 to 0.76) and 12 months (RR 0.43; 95% CI 0.27 to 0.69) (page 2, third paragraph).

Introduction Page 4, would it be useful to report compliance in the methods?
A: We did not mentioned compliance in the protocol, but based on the feedback we have decided to introduce compliance as a secondary outcome in the methods section. We have added the following sentence: “Compliance was not defined as an outcome in the original protocol, but following feedback, we included compliance as a secondary outcome post hoc.” (page 5, second paragraph)

The lack of efficacy long term may be due to decreased compliance Methods Page 4, would authors consider adding in a column on the compliance of compression stockings use if this is reported in the studies.

A: Thank you for pointing this out. In accordance with the previous comments, we have chosen to introduce ‘compliance’ as a secondary outcome in the methods section. Subsequently, we have added a new column in table 2 to present compliance data.

Including a column on intention to treat vs per protocol as one infers effectiveness and the other efficacy.

A: We understand this request, and we agree it could have been interesting to emphasize differences between ITT (calculated from all randomised participants) and per-protocol (calculated from all patients who comply with the treatment they are randomised to). Unfortunately, however, the calculation of ‘true’ ITT and per-protocol estimates is prevented by heterogeneous and incomplete reporting in the primary studies. One study (Clarcke-Moloney) reported that poor compliance was associated with lower effect. Two studies (Kapp and Nelson) stated there was no difference in the results for ITT and per protocol analysis, but without reporting data in sufficient detail to calculate ITT and per protocol estimates. Vandongene and Jungbeck have not reported available data for ITT analysis. We added a sentence in the discussion, but these findings were contradicted by studies reporting that the overall results did not change significantly when non-compliant patients were excluded from the analysis (page 13, first paragraph).

Results

Page 8, for the table, in the last column, it might be useful to report actual % of recurrence as well as relative risk to give the readers an idea of the actual rates.

A: The effect sizes are re-calculated and presented in absolute measures in table 3.
For the last row, last column; please indicate if the study was significant, the reader found out from page 10 that there was no difference between Grade 1 or Grade 2 stockings.

A: In table 2 we have added two asterisk (**) after statistically significant results.

(please include the findings of Jungbeck in the abstract).

A: We agree with this suggestion, and have revised the abstract accordingly (see page 2, third paragraph).

Page 9. Is skin break lasting more than 4-6 weeks an accepted definition of leg ulcer?

A: We have used the definition reported in the included studies.

Discussion

Page 11

Consider replacing "Swollen leg" with "symptoms of venous insufficiency".

A: After discussing your suggestion, we have ended up with not replacing swollen legs with symptoms of venous insufficiency. Then we have to replace the concept in the whole manuscript and it might be a problem related to too many words in the title.

Line 265 and 266 "uncertain". Rather than use uncertain, consider (line 265), a study has shown that stockings of higher compression grades (grade 3) were better than the medium grade (Grade 2).

A: We have revised the sentences like this: “The main finding is that compression stockings class 2 probably reduce the risk of leg ulcer recurrence compared to compression stockings class 1. One included study (20) suggests that stockings of higher compression (class 3) were better than medium compression (class 2), but the study only included 100 participants and overall evidence was assessed as having low quality. Therefore, it remains uncertain whether the use of stockings with higher compression grades is associated with a further risk reduction.” (page 11, second paragraph).
Line 265, you found a paper which stated that there was no difference in symptoms of Venous insufficiency in patients wearing Grade 1 or Grade 2 compression stockings. (you have found a paper - so you can quote it)

A: We agree, and now we refer to these findings at page 11, second paragraph.

Page 12 Consider adding a sentence in the introduction, "… Carvalho and Al Shammeri reported that by wearing compression stockings patients under 70 years old found improvement in symptoms of venous insufficiency. The effectiveness in not known in the older population.

A: Thank you for pointing this out. We have added the following sentence in the introduction: “Two studies (9,10) reported that by wearing compression stockings patients under 70 years old experienced improvement in symptoms of venous insufficiency, whereas the effectiveness is not known in older populations.” (page 4, paragraph 2).

The compliance paragraph showed be part of the results. (table) then in the discussion, you can refer to how difficult it is to maintain compliance, so while compression stockings are efficacious, the patients will not wear them long term - perhaps consider a different way of preventing recurrence of leg ulcer. You described the challenges of applying compression stockings on page 14 first paragraph

A: We agree that compliance is an interesting outcome. Based on the feedback from the reviewer we have now have added information about compliance in the result section (table 2) and added the following sentence in the discussion: “The same study reported that poor compliance was associated with lower effect (23), but these findings were contradicted by studies reporting that the overall results did not change significantly when non-compliant patients were excluded from the analysis (20, 22).” (page 13, first paragraph).

Reviewer 2: Astrid Stephan, Ph.D (Reviewer 2): Many thanks for the opportunity to review this interesting manuscript. The manuscript with the title "Effects of preventive use of compression stockings for elderly with chronic venous insufficiency and swollen legs: A systematic review and meta-analysis" reports a systematic review, which aims to identify the effect of compression stockings for elderly people. Though the systematic review seems to be well reported and conducted due to state of the art, some aspects needs to be clarified or considered.
Fundamental questions:

A recent Cochrane Review (Nelson et al. 2014) is mentioned, and the author did not find any further studies conducted since this review, or any ongoing trials. Moreover, the findings of the Cochrane review were confirmed. Thus, it does not become clear what the added value of this systematic review is. This needs to be better explained.

A: The Cochrane review of Nelson 2014 was published in 2014 and its literature search was performed in September 2014. Our literature search was performed in March 2018, about four and a half years later. As with regard to the claim that we did not identify any further studies, that is not correct. We included two new and well-conducted studies, i.e. Kapp (20) and Clarke-Moloney (23), implying that we present a wider evidence base. Furthermore, and as discussed below, our review also differs from the Cochrane review in that we focus on a geriatric population. We have added a new sentence to the introduction: “……., but a preliminary search showed that these systematic reviews were no longer up to date. Elderly patients with chronic venous insufficiency and multimorbidity are of particular interest because they frequently need assistance from home care personnel to administer compression stockings (page 4, paragraph 2).”

What was the rationale to include only people 70 years or older?

A: In clinical geriatric practice, it is common to include patients above 70 years, both in hospitals and in home care services. To our knowledge, patients below 70 years of age are not routinely admitted to geriatric services in any country today. In fact, patients who are treated within geriatric services tend to be considerably older, usually above 80 or even 85 years. As the title of the manuscript states, we wanted to focus on elderly people.

According to the flow chart, the authors excluded 17 studies due to population. Was this due to age restriction?

A: These studies were excluded according to the pre-defined selection criteria: 11 of 17 studies were excluded according to age whereas the remaining six studies were excluded because they dealt with treatment of ongoing leg ulcers. With regard to the latter category, the role of compression in the treatment of existing ulcers is much better documented than prophylactic use.
Within the discussion, section it is stated that effects revealed in a younger population may be transferred to elderly people as well (page 12, line 285-287). So it should be reasoned why an age-restriction was necessary in this review.

A: We support your comment and have therefor revised the sentence: “However, the patients in the latter studies were too young to be included in our review, and the applicability to a geriatric population can be questioned (page 12, paragraph 2).”

Minor, specific questions:

Abstract

It should be reported, which outcomes were investigated (primary and secondary), and "no findings" should be reported as well in the abstract.

A: As both of the reviewers have pointed this out, we have followed your suggestions (see comments to reviewer I, under abstract). Moreover, we have also added a sentence in the method section of the abstract stating: “Secondary outcomes were other health related outcomes e.g. pain, compliance.” (page 2, second paragraph).

Methods

Please start with a basic introduction of the methods applied. The registration of the protocol can be presorted later on, though it is the first bullet point in the PRISMA statement to be included in the methods, it does not read very well, I think.

A: We have added this sentence to the introduction: “This systematic review follows the recommendations of the Cochrane handbook of systematic reviews of interventions (page 4, third paragraph).

Was any other inclusion criteria applied? Such as language restriction, type of intervention or intervention components (additional counselling) and way of intervention delivery, for example support from home care organizations?

A: No other inclusion criteria were applied than already reported in the manuscript.

Why was mobility chosen as a primary main outcome? The rationale does not become quite clear and there is no discussion about mobility in the context of venous insufficiency provided.
A: We choose mobility as a primary outcome because mobility is an important skill for improving compliance and independence of compression stocking use.

How were data collected across the included five studies? This may be of importance since you include studies lasting up to five years.

A: We collected data as reported in the studies and according to the inclusion criteria. Two reviewers performed the data extraction independently. However, we are not sure if this answer your question.

Results

Caption of figure 2 is lacking

A: Kindly look at the upper right of the figure 2 at page 20- there is the caption.

It should to be reported whether compression was the only intervention applied or whether other intervention components, such as information or counselling, were provided.

A: We have followed your suggestion by adding reported information on additional intervention components. This additional information is found in the result section (page 7, second paragraph).

Since only 5 studies were include, more details regarding participants (gender, co-morbidity) and the application of the intervention would be desirable.

A: We have added more information regarding characteristic of the participants. See page 7 description of studies, second paragraph.

What does this sentence mean: "The studies compared different classes of compression and used different standards? However, we defined classes according to the European standard." (line 173-174, on page 7)

A: We understand the confusion, and have rephrased the sentence to: “Four studies (20, 21, 23, 24) used European standard for defining compression classes, and they compared different
grades of compression. One study (22) used British standard and we redefined this to European standard.” (page 7, second paragraph).

Discussion

The discussion should also include limitations.

A: We have revised the following sentence: “It is a limitation that the quality of the evidence was graded from moderate to very low, implying there is a need for further research on these topics before we can make a firm conclusion about the effects of preventive use of compression stockings.” (Page 13, third paragraph).

Conclusion

The conclusion needs to be specified since you only investigated elderly people.

A: This is important input, and we have revised the sentence according to the suggestion: “

Based on the results of this systematic review, medical compression stockings probably reduce leg ulcer recurrence up to one year in elderly people, but the effect after one year is unclear.” (See page 14, second paragraph).

Maybe I did not understand correctly or missed something, but wasn't it the case that you included only studies investigating leg ulcer recurrence?

A: According to our inclusion criteria, we included studies investigating compression stockings for prevention of ulcers (both ulcer and ulcer recurrence), thrombosis and mobility. However, the existing evidence base is mostly about prevention of ulcer recurrence.

Wouldn't it better to say that further evidence for effects on primary outcomes is lacking instead of scarce?

A: We have followed your suggestion (see page 14, second paragraph).