PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	EFFECTIVENESS OF BETA BLOCKERS IN PHYSICALLY ACTIVE PATIENTS WITH HYPERTENSION: PROTOCOL OF A SYSTEMATIC REVIEW
AUTHORS	Tuckova, Dagmar; Klugar, Miloslav; Sovova, Eliska; Sovova, Marketa; Stegnerova, Lenka

VERSION 1 - REVIEW

REVIEWER	Gavin WK Wong Cochrane hypertension group University of British Columbia Vancouver, Canada
REVIEW RETURNED	19-Dec-2015

GENERAL COMMENTS	The objective should include the comparator. The objective should be included in the abstract. Please describe the outcome of the stress test for readers who do not know much about stress test. Please list all the parameters you plan to extract in the outcome section. Dividing the list to dichotomous and continuous outcomes might help reader to get a better sense as what will be examined. Primary and secondary hypertension are different in many aspects. Depend on what kind of underline condition secondary hypertension may have, it might produce very different results compare to primary hypertension. If the authors wish to include secondary hypertension in the review, I recommend a sensitivity analysis for primary/secondary hypertension. I'm confused about the comparator described in type of intervention. I understand that authors are interested in comparing beta blocker mono-therapy to beta blocker in combination therapy? I'm confused by the phase "as a part of treatment", it seems to me that you mean combination therapy. Please clarify. Non RCT data should not be pooled with RCT data, even if it's quasi-randomized trial. They should be analysed separately and interpreted separately. The data from non-RCT data should not be considered at the same quality as data from RCT. Please define lack of robustness in sensitivity analysis.

REVIEWER	Sheldon Tobe University of Toronto and the Northern Ontario School of Medicine, Canada.
REVIEW RETURNED	03-Jan-2016

GENERAL COMMENTS	This manuscript is the protocol for a planed systematic review to see whether there is sufficient evidence to determine if certain beta blockers are less physically limiting for patients with hypertension who are active. The protocol outlines a process which will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 (PRISMA-P). While beta blockers are recommended and are commonly used for hypertension, there is confusion about their appropriate use because of meta-analyses of studies, largely using atenolol that have not demonstrated the benefits that were expected. Further, beta blockers are known to interfere with physical performance and exercise capacity. If certain beta blockers are better tolerated by active people with hypertension, and are still effective, then this information will be highly valuable for the millions of people who live with hypertension and require antihypertensive therapy. The main outcome listed for the study is performance on stress tests (maximal or submaximal). I am concerned that there may not be sufficient studies to perform statistical testing. However, the authors plan to do a very thorough search of the mainstream literature, trial registries, as well as additional data bases, grey literature and more detailed means such as searching through the references of identified studies, and assessing epidemiologic and case control studies if needed. Plans for review include appropriate review of abstracts and even double data entry, the creation of the risk of bias table. The statistical plan is appropriate as is the decision to use a fixed effect model for homogenous RCTs. There is a plan to assess subgroups as well as to do sensitivity and sub group analyses if there is significant heterogeneity. Will the sub group analyses be the same as those already listed, or were more planned? For the beta blocker dosing sub group analysis, do the authors feel that they will be able to get sufficient dosing information to be able to carry this out? It would be interesting if possible to compare vasodilating and non-vasodilating beta blockers as one of the sub group analyses.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Gavin WK Wong

Institution and Country
Cochrane hypertension group
University of British Columbia
Vancouver, Canada

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
The objective should include the comparator.
Our objective is to determine which beta blockers are less physically limiting for patients with hypertension who are physically active.
We assumed it was clear that we will look for studies which compare different beta-blockers.
However, we have changed our objective formulation to: The objective of this review is to determine by comparison of existing beta blockers (both mono and combination therapy) which are less physically limiting for patients with hypertension who are physically active.

The objective should be included in the abstract.
The objective was part of abstract a bit rephrased as aim, however, we have changed it to the same formulation as mentioned above.

Please describe the outcome of the stress test for readers who do not know much about stress test.
This information was added to the introduction section:
Exercise testing is used widely for the detection of coronary artery disease, prediction of cardiovascular events, evaluation of physical capacity an effort tolerance, evaluation of exercise-related symptoms, assessment of chronotropic competence, arrhythmias and response to implanted device therapy and assessment of the response to medical interventions (1). Current clinical exercise testing procedures involve predominant dynamic-aerobic component. Tread mill and cycle ergometers are the most commonly used dynamic exercise testing devices. Ventilatory expired gas analysis allows the measurement of minute ventilation, VO2 and VCO2 and the combination with ergometers is commonly known as cardiopulmonary exercise testing (CPX).
The 6-minutes’ walk test is a functional test that can be used to evaluate submaximal exercise capacity. This assessment is frequently used in patients with chronic disease, such as heart failure or chronic obstructive pulmonary disease (2).
VO2 max is the peak oxygen uptake achieved during the performance and it is considered the best measure of cardiovascular fitness and exercise capacity (3). Exercise capacity is the most powerful predictor of survival (1).

1. Fletcher GF, Ades PA, Kligfield P et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation 2013;128: 873-934.
2. ATS committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minutes walk test. AM J Respir Crit Care Med 2002; 166: 11-117.
3. Mc Ardle WD, Katch FI, Katch VL. Exercise Physiology: Nutrition, Energy and Human Performance. Baltimore, MD, Lippincott Williams and Wilkins. 2010.

Please list all the parameters you plan to extract in the outcome section. Dividing the list to dichotomous and continuous outcomes might help reader to get a better sense as what will be examined.
Beside parameters mentioned in the part data collection and outcomes, we do not know exactly what primary studies with what parameters will be retrieved for possible pooling.
We can assume that continuous data like VO2 peak, VO2 peak ml/kg/min, HR rest and peak, BP rest and peak, W, W/kg, RER, oxygen pulse, anaerobic threshold will be extracted.
We can also assume that some categorical data for example performance limitation and severity of comorbidities will be extracted.

Primary and secondary hypertension are different in many aspects. Depend on what kind of underline

condition secondary hypertension may have, it might produce very different results compare to primary hypertension. If the authors wish to include secondary hypertension in the review, I recommend a sensitivity analysis for primary/secondary hypertension.
Thank you for adding this comment and advice. In case of retrieving papers with both types of hypertension, we will perform another sub group analysis which will be focused on this aspect in the systematic review.

I'm confused about the comparator described in type of intervention. I understand that authors are interested in comparing beta blocker mono-therapy to beta blocker in combination therapy? I'm confused by the phase "as a part of treatment", it seems to me that you mean combination therapy. Please clarify.
Our objective is to find out less limiting beta blocker as if it is single therapy or monotherapy. So we may find out studies which compare different beta blockers as mono-therapy vs another beta blocker as monotherapy, or beta blockers as monotherapy vs another beta blockers as combination therapy or finally beta blockers as combination therapy vs another beta blockers as combination therapy.
We separated types of interventions and types of comparisons in the part study eligibility.

Non RCT data should not be pooled with RCT data, even if it's quasi-randomized trial. They should be analysed separately and interpreted separately. The data from non-RCT data should not be considered at the same quality as data from RCT.
Yes we completely agree, it was our plan that only studies with similar design will be pooled in meta-analyses.

Please define lack of robustness in sensitivity analysis.
We clarified it in the text:

The sensitivity analysis will be used to assess the robustness of the results to specific decisions made and methods used.
The more results obtained is materially unchanged by sensible sensitivity analyses, the more confident we will be in the final results of the meta-analysis.

Reviewer: 2

Reviewer Name
Sheldon Tobe

Institution and Country
University of Toronto and the Northern Ontario School of Medicine, Canada.

Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below
This manuscript is the protocol for a planed systematic review to see whether there is sufficient evidence to determine if certain beta blockers are less physically limiting for patients with hypertension who are active. The protocol outlines a process which will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 (PRISMA-P).

While beta blockers are recommended and are commonly used for hypertension, there is confusion about their appropriate use because of meta-analyses of studies, largely using atenolol that have not

demonstrated the benefits that were expected. Further, beta blockers are known to interfere with physical performance and exercise capacity. If certain beta blockers are better tolerated by active people with hypertension, and are still effective, then this information will be highly valuable for the millions of people who live with hypertension and require antihypertensive therapy.

The main outcome listed for the study is performance on stress tests (maximal or submaximal). I am concerned that there may not be sufficient studies to perform statistical testing. However, the authors plan to do a very thorough search of the mainstream literature, trial registries, as well as additional data bases, grey literature and more detailed means such as searching through the references of identified studies, and assessing epidemiologic and case control studies if needed.

Plans for review include appropriate review of abstracts and even double data entry, the creation of the risk of bias table. The statistical plan is appropriate as is the decision to use a fixed effect model for homogenous RCTs. There is a plan to assess subgroups as well as to do sensitivity and sub group analyses if there is significant heterogeneity.
Will the sub group analyses be the same as those already listed, or were more planned?
We plan to analyse the sub groups as they are mentioned after our revision in the protocol. However, there can be added some sub groups analysis additionally if necessary according to the information from primary studies. In this case, everything will be clearly and properly adjusted in the systematic review.
For the beta blocker dosing sub group analysis, do the authors feel that they will be able to get sufficient dosing information to be able to carry this out?
We never know exactly, what studies will be retrieved by extensive search. However, information about dosing would be important and interesting.

It would be interesting if possible to compare vasodilating and non-vasodilating beta blockers as one of the sub group analyses.
Thank you for the comment, yes, we think so too. Beta blockers have different pharmacodynamics and pharmacokinetic properties, so subgroup analysis will be used for hydrophilicity, lipophilicity, intrinsic sympathomimetic activity and vasodilatory properties.
We added it to the article.

VERSION 2 – REVIEW

REVIEWER	Gavin WK Wong Cochrane Hypertension group University of British Columbia Vancouver, Canada
REVIEW RETURNED	24-Feb-2016

GENERAL COMMENTS	Data synthesis Data from RCT should not be pooled with non-RCT data. Non-randomized trial should not be considered as the same quality as randomized trials. Consider revision in this section. Subgroup analysis Clinically, beta blockers are usually divided as nonselective, beta-1 selective, alpha and beta blocker, and partial agonist. The authors may consider performing subgroup analysis according to these categories, as they might be more relevant to clinicians.

	Meta-bias The authors might consider also using funnel plot to assess publication bias. Consult the Cochrane handbook for systematic review regarding the funnel plot.

VERSION 2 – AUTHOR RESPONSE

Data synthesis

Data from RCT should not be pooled with non-RCT data. Non-randomized trial should not be considered as the same quality as randomized trials. Consider revision in this section.

In the part of Data Synthesis, we considered your comment and we added sentence which will clarify that data from RCT will not be pooled with data from non-randomized trials or non-randomized trials.

Subgroup analysis

Clinically, beta blockers are usually divided as nonselective, beta-1 selective, alpha and beta blocker, and partial agonist. The authors may consider performing subgroup analysis according to these categories, as they might be more relevant to clinicians.

Thank you so much for comment in the part of Subgroup analysis. We consider your recommendation and we will pay attention to another sub group due to the category of the nature of beta blockers which are divided as nonselective, beta-1 selective, alpha and beta blocker, and partial antagonist. We added this information in the protocol.

Meta-bias

The authors might consider also using funnel plot to assess publication bias. Consult the Cochrane handbook for systematic review regarding the funnel plot.

Thank you for the comment. We already mention funnel plots in the protocol before. It is mentioned in the part Meta-bias assessment and in the protocol as well. For better clarity, we underlined it in the text.