PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pulmonary arterial hypertension associated with connective tissue disease: meta-analysis of clinical trials
AUTHORS	Kuwana, Masataka; Watanabe, Hiroshi; Matsuoka, Nobushige; Sugiyama, Naonobu

VERSION 1 - REVIEW

REVIEWER	Lorinda Chung, MD, MS Assistant Professor of Medicine Stanford University School of Medicine USA I have received honorarium from Gilead Sciences for participating in a CME presentation within the last year.
REVIEW RETURNED	06-May-2013

GENERAL COMMENTS	This study is a meta-analysis to evaluate the effect of PAH-specific treatments on exercise capacity in patients with PAH overall, and in patients with CTD-APAH. The authors found that PDE-5-inhibitors and prostacyclin analogues are effective in improving 6MWD in patients with PAH overall and with CTD-APAH, however, endothelin receptor antagonists may result in a lesser improvement in the latter group. Additional analyses, if possible, would be helpful to clarify which patients/groups the results are most applicable to. 1. Pg 7--please define the exclusion criteria for studies more specifically so readers can understand why certain studies were excluded (ie. ARIES-2). 2. Pg 8--recommend listing the specific outcomes that were extracted. 3. Since SSc-PAH patients do worse than other CTD-APAH patients, is it possible to do a sensitivity analysis with just SSc-APAH patients? 4. Can analyses be repeated excluding open-label studies?

REVIEWER	Jeffrey A. Bakal, PhD., P.Stat. Lead, Health Research Methods and Analytics Alberta Health Services \ Sr. Biostatistician CVC Faculty of Medicine and Dentistry Li Ka Shing Centre for Health Research Innovation University of Alberta

	No competing interests
REVIEW RETURNED	10-May-2013

THE STUDY	The statistical analysis section could use some expansion as there is little description on what was done. There is no mention if there was any weighting of the trials or how that was determined. The comparison of the outcome measure is a little hard to follow.
RESULTS & CONCLUSIONS	There is a comparison of trials but the paper seems to be stuck between being a review and a meta analysis, making it difficult to know if we should be looking at a single result or the combination. This makes it difficult for me at least to determine what the take home message is
GENERAL COMMENTS	IN the presentation of the results and summaries the range of means is confusing as it gives the reader that it is a range of subject level values rather than means of means. Also given the differences is sizes/weigthings of studies this presentation makes it difficult to understand. Additionally the I^2 statistic is only mentioned in the methods but there is nowhere I could see that it was actually used, nor what would be done if it was significant.

REVIEWER	Paul M. Hassoun, MD Professor of Medicine Director, Pulmonary Hypertension Program Johns Hopkins University I have no competing interests with the current study.
REVIEW RETURNED	11-May-2013

GENERAL COMMENTS	Kunawa et al performed a meta-analysis of studies evaluating efficacy of pulmonary arterial hypertension (PAH) treatment in general (19 studies) and with a specific focus on connective tissue disease (CTD) associated PAH (9 studies) in order to compare the effects of current pulmonary vasoactive PAH agents in these two groups. A total of 3073 (all PAH) and 678 (CTD-PAH) patients were included in this analysis. The primary outcome measure was the change in the 6 minute walk distance (6MWD) compared to placebo values. Their analysis indicates that all types of agents were effective for PAH, however, endothelin receptor antagonists (ERAs) appeared less effective against CTD-PAH. General: The authors address an important clinical question, i.e., the efficacy of modern PAH therapy in patients with CTD-PAH. Although CTD-PAH represents the largest group of patients

	with associated PAH in group 1, no large therapeutic study has focused on this particular group. Therefore, the work presented here is important. The findings that current agents may improve the 6MWD in CTD-PAH, but less so compared to other PAH patients, are not too surprising. The choice of studies (randomized clinical trials (RCTs) and open-label, single arm trials considering the paucity of studies on this topic), search engines and key terms all appear adequate. The studies are appropriately weighted. Interpretation of data and the discussion are informative and well balanced, respectively. The manuscript is in general well written and provides a useful assessment of the current efficacy of therapy in CTD-PAH patients. Figures 1-3 are clear and adequately reflect the data.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Lorinda Chung, MD, MS
Assistant Professor of Medicine
Stanford University School of Medicine
USA

I have received honorarium from Gilead Sciences for participating in a CME presentation within the last year.

This study is a meta-analysis to evaluate the effect of PAH-specific treatments on exercise capacity in patients with PAH overall, and in patients with CTD-APAH. The authors found that PDE-5-inhibitors and prostacyclin analogues are effective in improving 6MWD in patients with PAH overall and with CTD-APAH, however, endothelin receptor antagonists may result in a lesser improvement in the latter group. Additional analyses, if possible, would be helpful to clarify which patients/groups the results are most applicable to.
1. Pg 7--please define the exclusion criteria for studies more specifically so readers can understand why certain studies were excluded (ie. ARIES-2).

Answer
Thank you for your valuable comments.
• We have added further details about the exclusion criteria to the second paragraph under the Eligibility heading in the Methods on page 7.
• Data from ARIES-2 are actually included in this meta-analysis, because Galiè et al. (2008)23 presents data from both ARIES-1 and ARIES-2.

2. Pg 8--recommend listing the specific outcomes that were extracted.

Answer
• The outcomes (mean difference, m and 95%CI, m or standard error) that were extracted from each study are now specified in parentheses under the heading Data collection in the Methods on page 8, as requested. The actual values of the outcomes are presented on the

right sides of figures 2 and 3, and summarized under the headings “6MWD in All PAH patients” and “6MWD in a subgroup of CTD-PAH patients” in the Results.

3. Since SSc-PAH patients do worse than other CTD-APAH patients, is it possible to do a sensitivity analysis with just SSc-APAH patients?

Answer
• We agree that it would have been interesting to do a sensitivity analysis with the data from SSc-PAH patients only, but this is not possible for the following reasons. There are only two articles (Launay et al., 201036 and Badesch et al., 200026) from which data for the subpopulation of SSc-PAH patients can be extracted. In other articles listed in Table 2, data for the SSc-PAH subpopulation were not presented. This is now mentioned in the Discussion as a limitation of our study.

4. Can analyses be repeated excluding open-label studies?

Answer
• We did an additional sensitivity analysis excluding open-label single-arm studies for CTD-PAH patients only. The results are shown in the attached figure, which we submit for publication as supplementary material. We have the following paragraph under the 6MWD in a subgroup of CTD-PAH patients heading of the Results:
‘We did an additional sensitivity analysis excluding open-label single-arm studies for CTD-PAH patients only (supplementary figure). The overall estimate of mean difference between changes in 6MWD in patients with CTD-PAH was 37.2 m (95%CI 25.0 to 49.3 m, I2=20.5%) and the ranges of mean differences by subgroup of patients receiving PDE-5 inhibitors, ERAs, and PGI2 analogues were 37.0−47.1 m, 19.0−22.1 m, and 21.0−108.0 m, respectively.’
We included the study by Badesch et al. (2000)26 in this additional sensitivity analysis, because there is only one randomised controlled trial for epoprostenol in CTD-PAH patients.
• Please note that there was no double-blind study for epoprostenol. The three studies24−26 for epoprostenol and one study29 for iloprost for all forms of PAH were all open-label randomised controlled trials. Therefore we did a sensitivity analysis for CTD-PAH patients only but not for patients with all forms of PAH.

Reviewer: Jeffrey A. Bakal, PhD., P.Stat.
Lead, Health Research Methods and Analytics Alberta Health Services \ Sr. Biostatistician CVC Faculty of Medicine and Dentistry
2-132 Li Ka Shing Centre for Health Research Innovation University of Alberta -No competing interests

The statistical analysis section could use some expansion as there is little description on what was done. There is no mention if there was any weighting of the trials or how that was determined.

The comparison of the outcome measure is a little hard to follow.
There is a comparison of trials but the paper seems to be stuck between being a review and a meta analysis, making it difficult to know if we should be looking at a single result or the combination. This makes it difficult for me at least to determine what the take home message

is.

In the presentation of the results and summaries the range of means is confusing as it gives the reader that it is a range of subject level values rather than means of means. Also given the differences is sizes/weigthings of studies this presentation makes it difficult to understand.

Additionally the I^2 statistic is only mentioned in the methods but there is nowhere I could see that it was actually used, nor what would be done if it was significant.

Answer
Thank you for your valuable comments.
We have revised our manuscript based on your suggestions as follows.
• As requested, we have expanded the Statistical analysis section of the Methods. Regarding the weighting of studies, we used the DerSimonian−Laird method, as now described.
• We think that the pooled mean difference of each PAH agent is preferable when interpreting the results. We have revised our manuscript to clarify that the means in the text are the pooled means.
• We have added I2 values to the Results section.

Reviewer: Paul M. Hassoun, MD
Professor of Medicine
Director, Pulmonary Hypertension Program Johns Hopkins University

I have no competing interests with the current study.

Kunawa et al performed a meta-analysis of studies evaluating efficacy of pulmonary arterial hypertension (PAH) treatment in general (19 studies) and with a specific focus on connective tissue disease (CTD) associated PAH (9 studies) in order to compare the effects of current pulmonary vasoactive PAH agents in these two groups. A total of 3073 (all PAH) and 678 (CTD-PAH) patients were included in this analysis. The primary outcome measure was the change in the 6 minute walk distance (6MWD) compared to placebo values. Their analysis indicates that all types of agents were effective for PAH, however, endothelin receptor antagonists (ERAs) appeared less effective against CTD-PAH.

General:

The authors address an important clinical question, i.e., the efficacy of modern PAH therapy in patients with CTD-PAH. Although CTD-PAH represents the largest group of patients with associated PAH in group 1, no large therapeutic study has focused on this particular group. Therefore, the work presented here is important. The findings that current agents may improve the 6MWD in CTD-PAH, but less so compared to other PAH patients, are not too surprising.

The choice of studies (randomized clinical trials (RCTs) and open-label, single arm trials considering the paucity of studies on this topic), search engines and key terms all appear adequate. The studies are appropriately weighted.

Interpretation of data and the discussion are informative and well balanced, respectively. The manuscript is in general well written and provides a useful assessment of the current efficacy of therapy in CTD-PAH patients. Figures 1-3 are clear and adequately reflect the data.

Answer
Thank you for your valuable comments.

VERSION 2 – REVIEW

REVIEWER	Lorinda Chung, MD, MS Assistant Professor of Medicine Division of Immunology and Rheumatology Stanford University School of Medicine I have received honorarium from Gilead Sciences for participating in a CME presentation within the last year.
REVIEW RETURNED	12-Jun-2013

THE STUDY	the supplemental documents do not raise questions about the work.
GENERAL COMMENTS	The authors have addressed all reviewer comments.

REVIEWER	Jeffrey A. Bakal, PhD., P.Stat. Lead, Health Research Methods and Analytics Alberta Health Services /University of Alberta
REVIEW RETURNED	26-Jun-2013

- The reviewer completed the checklist but made no further comments.