PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Tolvaptan Add-on Therapy in Patients with Acute Heart Failure: Meta-analysis on Randomized Controlled Trials
AUTHORS	Ma, Guang; Ma, Xixi; Wang, Guoliang; Teng, Wei; Hui, Xuezhi

VERSION 1 - REVIEW

REVIEWER	Keisuke Kida Department of Cardiology, St. Marianna University School of Medicine, Kawasaki, Japan
REVIEW RETURNED	14-Sep-2018

GENERAL COMMENTS	Ma and colleagues reported the findings of "Effects of Tolvaptan add-on therapy in patients with acute heart failure: meta analysis of randomized controlled trials". The principal finding of the study is that comparing with the standard diuretic therapy, Tolvaptan add-on therapy did not reduce the incidence of worsening renal function and short-term mortality, however, can decrease body weight and elevated sodium level in patients with acute heart failure. This is a quite interesting meta analysis paper that addresses a unique data obtained from the patients with acute heart failure. However, there are significant concerns about their study as described below. 1. The baseline characteristics of each study are summarized in Table 1. The authors showed the LVEF data, except one study by Jujo et al [23]. However, they demonstrated the LVEF data in the supporting information (Table S1). 2. The authors showed the study location as Japan and America by Matsue et al [18]. However, the AQUAMARINE study was a multi center at 14 hospitals across Japan. 3. The authors showed the follow-up duration as 636 days by Matsue et al [18]. However, the primary end point of the AQUAMARINE study was amount of urine output within 48 hours after randomization. The combined end point of all-cause death and heart failure rehospitalization within 90 days. 4. The authors analyzed the effects of tolvaptan with or without carperitide on WRF. However, the doses of tolvaptan were 30mg in the two studies in the US and 15mg or less in the studies other than the US. The authors should analyze the effects of tolvaptan dose on WRF.

REVIEWER	Yugo Shibagaki St Marianna University, Japan
REVIEW RETURNED	28-Sep-2018

GENERAL COMMENTS	Guang et al reported the meta analysis of RCT of tolvaptan for acute heart failure. The manuscript was made according to the PRISMA appropriately. 1. Although the systematic review was done for the paper published until October 2017, an important RCT was published in December 2017 (Inomata T, et al. Circ J 2017; 82: 159-167). I would recommend to include this study to strengthen your paper. 2. It looks like that the results from Japanese studies are different from those of western studies. Doses were different between those studies with positive and negative results for renoprotection? How do authors speculate this discrepancy.

REVIEWER	Luis Angel Pérula de Torres Teaching Unit of Family and Community Medicine of Córdoba. Sanitary district Cordoba and Guadalquivir. Andalusian Health Service, Cordoba, Spain
REVIEW RETURNED	21-Oct-2018

GENERAL COMMENTS	-Formal aspects: the manuscript should be carefully reviewed to try to improve the syntax and the writing. The acronyms used, such as SMD in the abstract, should be explained. Avoid abusing the use of too many acronyms, especially if they are not going to be used several times throughout the manuscript. -Statistical analysis: in the methodology, when it says "According to the Cochrane Handbook, ...", accompany the comment of a bibliographic citation. The estimators of the magnitude of the effect employed must be described (OR, differences of means, ...). -Results: the data and values in relation to the effect of Tolvaptan on sodium levels should be expressed, preferably in a forest plot, as has been done with the other end-point variables. -Other results of interest: The adverse effects of Tolvaptan were taken into account ?. If this could not be measured, comment on the limitations of the study. -Tables: Table 1 should look clearer and more orderly. The acronyms and the meaning of the data provided must be explained (mean, standard deviation?).

VERSION 1 – AUTHOR RESPONSE

Responds to the Reviewer #1

Competing interests: None declared.

Comment 1: The baseline characteristics of each study are summarized in Table 1. The authors showed the LVEF data, except one study by Jujo et al [23]. However, they demonstrated the LVEF data in the supporting information (Table S1).

Response 1: Thanks for suggestion. We present the results in Table 1. Please see the Results part.

Comment 2: The authors showed the study location as Japan and America by Matsue et al [18]. However, the AQUAMARINE study was a multi center at 14 hospitals across Japan.

Response 2: Thank you for pointing this out.We may have a wrong understanding of instructors of authors.We have deleted America in Table 1.

Comment 3: The authors showed the follow-up duration as 636 days by Matsue et al [18]. However, the primary end point of the AQUAMARINE study was amount of urine output within 48 hours after randomization. The combined end point of all-cause death and heart failure rehospitalization within 90 days.

Response 3: Thanks for your advice.In meta analysis the study articles[19-21] defined as one Randomized Controlled Study[20].Meta analysis included the studies with the longest follow-up time.Only this study had long-term follow-up results, and no other study had similar results.Not all results are included in the Meta analysis.

19. Matsue Y, Suzuki M, Nagahori W, et al. Clinical effectiveness of tolvaptan in patients with acute decompensated heart failure and renal failure: design and rationale of the AQUAMARINE study. Cardiovascular drugs and therapy 2014;28(1):73-7 doi: 10.1007/s10557-013-6491-8[published Online First: Epub Date]|.

20. Matsue Y, Suzuki M, Torii S, et al. Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction. Journal of cardiac failure 2016;22(6):423-32 doi: 10.1016/j.cardfail.2016.02.007[published Online First: Epub Date]|.

21. Matsue Y, Suzuki M, Torii S, et al. Prognostic impact of early treatment with tolvaptan in patients with acute heart failure and renal dysfunction. International journal of cardiology 2016;221:188-93 doi: 10.1016/j.ijcard.2016.07.063[published Online First: Epub Date]|.

Comment 4: The authors analyzed the effects of tolvaptan with or without carperitide on WRF. However, the doses of tolvaptan were 30mg in the two studies in the US and 15mg or less in the studies other than the US. The authors should analyze the effects of tolvaptan dose on WRF.

Response 4: Thanks for your advice.We made a subanalysis on differences in tolvaptan dose.The dose of tolvaptan may be related to the incidence of WRF. This result should be carefully interpreted, however, because the limitaion of present data(p=0.05), so more well-designed randomized clinical trials are needed.We delete the the effects of tolvaptan with or without carperitide on WRF.

Responds to the Reviewer #2

Competing interests: None declared.

Comment 1: Although the systematic review was done for the paper published until October 2017, an important RCT was published in December 2017 (Inomata T, et al. Circ J 2017; 82: 159-167). I would recommend to include this study to strengthen your paper.

Response 1: Thanks for your advice.This study can not met with the inclusion criteria. This study(Inomata T, et al. Circ J 2017; 82: 159-167) include patients suffered from moderate HF, with

New York Heart Association (NYHA) Functional Class II–III.The inclusion of this meta-analysis is that patients with ADHF.This study can not met with the inclusion.

Comment 2: It looks like that the results from Japanese studies are different from those of western studies. Doses were different between those studies with positive and negative results for renoprotection? How do authors speculate this discrepancy.

Response 2: Thanks for your advice.We made a subanalysis on differences in tolvaptan dose.The dose of tolvaptan may be related to the incidence of WRF. This result should be carefully interpreted, however, because the limitaion of present data(p=0.05), so more well-designed randomized clinical trials are needed. The body size, body weight, and treatment plan might influenced the results.

Responds to the Reviewer #3

Competing interests: None declared.

Comment 1: Formal aspects: the manuscript should be carefully reviewed to try to improve the syntax and the writing. The acronyms used, such as SMD in the abstract, should be explained. Avoid abusing the use of too many acronyms, especially if they are not going to be used several times throughout the manuscript.

Response 1: Thanks for your advice.The acronyms has been explained.

standardized mean difference (SMD)

mean difference (MD)

Pooled Relatives Risks (PRs)

Comment 2: Statistical analysis: in the methodology, when it says "According to the Cochrane Handbook, ...", accompany the comment of a bibliographic citation. The estimators of the magnitude of the effect employed must be described (OR, differences of means, ...).

Response 2: Thanks for your advice.We have added bibliographic citation in the Citation part and described the estimators of the magnitude of the effect employed in the manuscript.

16. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking

Meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews

of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Available from www.cochrane-handbook.org.

Comment 3: Results: the data and values in relation to the effect of Tolvaptan on sodium levels should be expressed, preferably in a forest plot, as has been done with the other end-point variables.

Response 3: Thanks for your advice.We have added it in the Results part. A funnel plot is also presented in the manuscript.As shown in figure 6.

Comment 4: Other results of interest: The adverse effects of Tolvaptan were taken into account ?. If this could not be measured, comment on the limitations of the study.

Response 4: Thanks for your advice.We have added the other adverse effects in the limitations part.

Comment 5:Tables: Table 1 should look clearer and more orderly. The acronyms and the meaning of the data provided must be explained (mean, standard deviation?).

Response 5:Thanks for your advice.We have added the meaning of the data in the Table1.

VERSION 2 – REVIEW

REVIEWER	Keisuke Kida Department of Pharmacology, St. Marianna University School of Medicine, Kawasaki, Japan
REVIEW RETURNED	26-Jan-2019

GENERAL COMMENTS	This revised version is substantially improved.

REVIEWER	Yugo Shibagaki St Marianna University, Japan
REVIEW RETURNED	12-Jan-2019

GENERAL COMMENTS	All the comments are clearly answered. No further comments.