

Format for ANSWERING REVIEWERS



July 28, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4266-review.doc).

Title: Hyponatremia in patients with heart failure

Author: Filippatos TD, Elisaf MS

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 4266

The manuscript has been improved according to the suggestions of reviewers:

REVIEWER 1

This is an interesting review on an important issue that is commonly present in the daily clinical practice. Nevertheless, in my opinion, some clarifications and addition are needed before the paper may be accepted for publication.

1. There sympathetic system is a major activator RAAS, but this concept is not so clear in the paper. In particular, in the following sentence " Patients with heart failure also exhibit enhanced activity of the sympathetic nervous system, which causes renal vasoconstriction and decreases glomerular filtration rate, and of the renin-angiotensin-aldosterone system, resulting in increased sodium and water retention and increased levels of AVP[35-42]."

We now present more clearly the mechanisms involved in the pathogenesis of hyponatremia in heart failure, defining the role of sympathetic nervous system (pages 4 and 5).

2. The authors should further emphasize the harmful effects of hyponatremia hypercorrection, describing the clinical characteristics of osmotic myelinolysis.

We added a paragraph describing the clinical characteristics of central pontine myelinolysis related to the rapid correction of hyponatremia (page 8).

3. It should be mentioned the recent warning on the potential hepatotoxicity of tolvaptan.

We added this important information regarding the potential hepatotoxicity of tolvaptan (page 13).

4. Finally, I think that tables or graphs reporting the mechanism underlying hyponatremia in heart failure, such as the different therapeutic options, including vaptans, could make the paper more intelligible.

We added a figure showing the mechanisms of hyponatremia in patients with heart failure and a table presenting the treatment options in patients with heart failure and hyponatremia.

REVIEWER 2

Excellent review regarding hyponatremia in patients with heart failure.

We thank the reviewer for his kind comments.

REVIEWER 3

Suggest the article title would better fit the content emphasis and that is the newer treatment of hyponatremia in CHF. The article is a review, limited by few newer studies and some studies with results still pending.

In our opinion the general title "Hyponatremia in patients with heart failure" is more appropriate for this minireview, since mechanisms of the pathogenesis of hyponatremia as well as the effects of hyponatremia on morbidity/mortality are also briefly presented. However, if the editor also thinks that the title should be changed, we could use the title "Newer treatment options for hyponatremia in patients with heart failure". Hyponatremia in heart failure is a condition known for decades, but with only a few large clinical studies. In this review, along with the established information, we present the new clinical studies regarding the effects of hyponatremia in the morbidity/mortality of patients with heart failure and the role of vaptans, as well as we briefly describe new molecules that may play significant role in the prognosis or development of hyponatremia such as copeptin and apelin.

The manuscript has been checked by a native English speaker and changes have been made accordingly.

Thank you again for publishing our manuscript in the *World Journal of Cardiology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'E. Elisaf', with a long horizontal flourish extending to the right.

Professor Moses S. Elisaf MD, FRSH, FASA, FISA

Department of Internal Medicine, School of Medicine, University of Ioannina,

Staurou Niarchou Avenue,

45 110 Ioannina, Greece

Phone: +30-26510-07509

Fax: +30-26510-07016

e-mail: egepi@cc.uoi.gr