



August 31, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 19779-REVIEW.doc).

Title: Therapeutic Modification of Arterial Stiffness: An Update and Comprehensive Review

Author: Ching-Fen Wu, Pang-Yen Liu, Tsung-Jui Wu, Yuan Hung, Shih-Ping Yang, Gen-Min Lin

Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 19779

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) **Reviewer 1:** In their manuscript Wu et al. review the possibilities of therapeutic modification of arterial stiffening. The subject is very exciting and in most of the fields authors managed to reach good quality. However, in some parts it has weaknesses.

1. However chronic kidney disease is on the list of table 1., but the active role of bone metabolism regulators in the development of arterial stiffening in CKD, a very exciting pathophysiological process, would be worth to be summarized in a few sentences¹.

Response: Thank you very much for your great comments. According to the suggested reference 1, we added a paragraph describing the association between CKD and arterial stiffness on lines 2-15, page 8.

2. The chapter "Measurement of arterial stiffness" discusses only two methodologies, which is far from the reality. At least shortly other methods should also be mentioned, see table 3 of².

Response: According to your suggested reference 2, we further mentioned other methods for evaluating arterial stiffness on the last 5 lines, page 10 to the end of page 11. In addition, table 2 was added to summarize several currently used measurements of arterial stiffness.

3. In chapter "Pharmacological therapy" authors should mention the phosphate binder sevelamer, which was found in ESRD patients to improve arterial stiffening³. Alagebrium, a AGE crosslink breaker should also be mentioned, as it is a promising agent, but clinical trials were not conducted because of financial problems of the developing company. In animal studies it improved arterial stiffness, which effect was missing in a small group of older individuals^{4, 5}. From this chapter I also miss the mention of any ongoing trials or future directions.

Response: According to your suggested references 3-5, we described these pharmacological interventions and some ongoing trials to improve arterial stiffness on lines 13-23, page 16.

4. Other grammatical remarks:

Page 5, line 17: "pathophysiology"

Page 6, line 6: "resistance muscular arteries"

On page 6, line 13 a reference should be cited about the changes of reflection point.

Figure 2 legends: "chemical stress"

Figure 2: There is a "u" character on an arrow.

In the legend of table 1 and throughout the paper: "lifestyle".

Reference 72: 56. is probably unnecessary

Response: Thank you very much. All these grammatical remarks have been corrected.

References:

- [1] Nemcsik, J, Kiss, I and Tisler, A, Arterial stiffness, vascular calcification and bone metabolism in chronic kidney disease, *World journal of nephrology*, 2012;1:25-34.
- [2] Boutouyrie, P, Fliser, D, Goldsmith, D, et al., Assessment of arterial stiffness for clinical and epidemiological studies: methodological considerations for validation and entry into the European Renal and Cardiovascular Medicine registry, *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2014;29:232-239.
- [3] Othmane Tel, H, Bakonyi, G, Egresits, J, et al., Effect of sevelamer on aortic pulse wave velocity in patients on hemodialysis: a prospective observational study, *Hemodialysis international. International Symposium on Home Hemodialysis*, 2007;11 Suppl 3:S13-21.
- [4] Oudegeest-Sander, MH, Olde Rikkert, MG, Smits, P, et al., The effect of an advanced glycation end-product crosslink breaker and exercise training on vascular function in older individuals: a randomized factorial design trial, *Experimental gerontology*, 2013;48:1509-1517.
- [5] Steppan, J, Tran, H, Benjo, AM, et al., Alagebrium in combination with exercise ameliorates age-associated ventricular and vascular stiffness, *Experimental gerontology*, 2012;47:565-572.

Response: All these references have been cited in the manuscript.

(2) **Reviewer 2:** I have reviewed the manuscript by Ching-Fen Wu and colleagues with interest. I found that this is basically well-written. I have following comments.

1. In the Introduction section, many descriptions regarding arterial stiffness should be supported by citations.

Response: Thank you very much to your great comments. We have cited some references to describe arterial stiffness in the introduction.

2. In the Measurement of arterial stiffness section, authors failed to discuss regarding Cardio-Ankle Vascular index (CAVI). Please add discussion regarding CAVI and whether pharmacological or non-pharmacological intervention can modify CAVI or not.

Response: We have added the part of CAVI following the pre-existed PWV methods on lines 9-24, page 16. In addition, with regard to the effect of non-pharmacological intervention on CAVI has been added on lines 7-9, page 12; line 11, page 13; lines 8-10, page 14; and the effect of pharmacological intervention on CAVI has been added on lines 4-6, page 16, in the section of **“Therapeutic modification of arterial stiffness”**

3. In the Measurement of arterial stiffness section, please discuss merit and demerit of several types of arterial stiffness parameters and consider to add Table comparing these arterial stiffness parameters including CAVI. 4. In Table 1, citations should be added for each factor.

Response: We compared the advantages and disadvantages among several types of arterial stiffness parameters on the last 5 lines, page 10 to the end of page 11 in the **“Measurement of arterial stiffness”** section. In addition, table 2 was added to summarize several currently used measurements for arterial stiffness. In table 1, the citations have been added.

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

Sincerely yours,

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