Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7219-review.doc).

Title: Therapeutic Interventions for Heart Failure with Preserved Ejection Fraction – A Summary of Current Evidence

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Name of Journal: *World Journal of Cardiology*

ESPS Manuscript NO: 7219

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 reviewers. These changes have been tracked highlighted.

3 References and typesetting were corrected.

4 A point to point discussion of reviewers' suggestions:

Reviewer #1 (00227550)

1. Scholarly review about treatment of heart failure with preserved ejection fraction. Presented in a professional way. I just suggest a change. Please check Page 4 last sentence of first paragraph. As far as I know action of nitrates are performed via nitric oxide not nitrogen nitrate.

Answer:
Thank you. This typo has been corrected under the heading "venous pressure reduction" – first paragraph, last line.

Reviewer #2 (00227540)

1. Only one thing to be considered that Newer agents such as angiotensin receptor neprilysin inhibitor, sildenafil, aldosterone antagonists and ivabradine sould be discussed briefly.

Answer:

1. Angiotensin receptor neprilysin inhibitor has been added in the "emerging therapies" section.
2. "Phosphodiesterase-5 inhibition" ie Sildenefil has been added in the "emerging therapies" section.
3. A paragraph on spironolactone has been added under the heading of "Venous pressure reduction"
4. Ivabradine has been added in the "emerging therapies" section.

Reviewer #3 (00214261)

1. In the section "venous pressure reduction", you may need to provide some references.

Answer:
References have now been provided.

2. On page 5, second last line, condition was spelled wrong.

Answer:
Corrected. Under the heading "Specific therapeutic agents" – line 4

3. On page 6, under ACE inhibitor, you need to provide citations for the "other studies".

Answer:
Provided now.

4. It is equally important to mention negative studies. This is exemplified by the section "Angiotensin Receptor Blockers", where you need to mention the I-PRESERVE study.

Answer:
Thank you. I-PRESERVE trial has now been mentioned in the "Angiotensin receptor blockers (ARB)" section.

5. On page 8, under Exercise Training, you should distinguish which studies examined HFPEF.

Answer:
References have been added.

6. With regard to agents used, you may want to mention the results of the TOPCAT study which show no benefit of MRA in HFPEF. The results were presented at the AHA but not published yet.

Answer:
It has been added in the "venous pressure reduction" section.

Reviewer #4 (00060499)

1. Introduction is very brief.....even though the topic is therapeutic intervention there should be some mention of what is HFPEF...please define... with reference.....most important is to mention first what is known till now regarding this problem.....and why you are now writing this review.....what is the importance or rationale of knowing or discussing the therapeutic interventions..... some more details is needed regarding its prevalence specifically quoting registries....what are the specific etiology and risk factors.....briefly....what is its morbidity and mortality.....again with reference.

Answer:
Although the basic aim of this article was to focus on therapeutic interventions and not HFPEF overall, its definition and a brief discussion of its prevalence, aetiology, risk factors,

morbidity, mortality, and rationale for this article has been added in the "introduction section", as per the reviewer's suggestion.

2. Revisit this term.....systolic heart failure (SHF).....any other new term for it??

Answer:
It has been replaced with heart failure with reduced ejection fraction (HFREF)

3. Treating the hypertension.....is controversial but not discussed in detail.....please review 5-10 trials which have shown exactly whether treating hypertension improves diastolic dysfunction or not. What parameters in diastolic function including TDI parameters [E/E' etc..] changed pre and post control of hypertension. Which regimen improves diastolic function the most? Controversial? Most of us presume that controlling hypertension improved diastolic function....but how? How much? How to assess in day to day practice? I do not agree that all antihypertensive have same effect....then why BB is not the preferred ones now? What did HACVD study show? Is aggressive control same as standard control....what targets?? What did EXCEED trial show? Any relation with BNP. Furthermore, many studies have shown that the effects of lowering blood pressure, either with an ACE or with any other anti-hypertensive drug, do not seem to markedly improve diastolic function.....Hence treating hypertension will not definitely improve diastolic function.... even if it improves...may not improve clinical symptoms. In addition, large randomized clinical trials showed limited effects of ACE-inhibitors, angiotensin receptor blockers, or beta-blockers, on clinical outcome in patients with HFPEF.CHARM-PRESERVE, I-PRESERVE, PEP CHF etc

Answer:

1. A detailed discussion has been added with a review of important trials to shown exactly whether treating hypertension improves diastolic dysfunction or not.
2. Changes in echo arameters including TDI have been included
3. Regimen inludedin the trials have been mentioned.
4. A differential effect of various antihypertensives in different trials has been discussed.
5. Impact of control intensity including HACVD and EXCEED trials has been discussed.
6. A further discussion on individual agents (ACE-inhibitors, angiotensin receptor blockers, or beta-blockers) and their impact on clinical outcomes including CHARM-PRESERVE, I-PRESERVE, PEP CHF trials has been given in the later part of the article.

4. Controlling the heart rate.....very briefly written.....why it is important to control heart rate?? What are the mechanisms in diastolic dysfunction and HFPEF?? BB role in grade III/IV diastolic dysfunction is controversial as these patients are dependent of high heart rate...they may go into cardiogenic shock when you give BB.....should mention about that with references.....calcium antagonists are shown to improve diastolic function only during exercise. So what is ideal resting heart rate and exercise heart rate?? Role of Ivabradine in HFPEF??

Answer:
A detailed discussion has now been included. Role of Ivabradine has been discussed separately under "emerging therapies" section.

5. 'Atrioventricular node ablation with subsequent pacemaker implantation may be

considered in patients where achieving sinus rhythm is considered an important goal.'.....very confusing statement.....how does AVN ablation and PCM achieve sinus rhythm. Are you referring to patients with long AV delay or IVCD in sinus rhythm? Please elaborate and give references.

Answer:
This line has been removed.

6. ACE INHIBITORS/ARB.....very very superficial discussion.....need to mention with name all the landmark studies which I mentioned above with their results and discuss in detail.

Answer:
Detailed discussion along with mentioned trials has been added (sections: hypertension, ACei, ARBs)

7. BB....authors give a wrong message telling Nevibilol is good in HFPEF.....should go in depth and categorize diastolic dysfunction grades I/II/III/IV and discuss the use of BB and other drugs in each, Very superficially written.

Answer:
SENIORS trial has been discussed for nebivolol. Further discussion added as per recommendations.

8. CA antagonists/ Digoxin.....repeat discussion....delete.

Answer:
1. CCB section deletd.
2. Digoxin discussion deleted from the "heart rate control" section.

9. What about aldosterone antagonists, gene therapy, surgery, natriuretic peptides, endothelin blockers, NO donors ...totally excluded?

Answer:
1. aldosterone antagonists discussion added in the sections:
    a. hypertension
    b. venous pressure reduction
2. gene therapy has been added under "emerging therapies"
3. phosphodiesterase-5 and endothelin inhibition has been added under "emerging therapies"
4. NO donors have been added under "emerging therapies"

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

Sincerely yours,

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