Author’s response to reviews

Title: Relationship between drug application and mortality rate in Chinese older coronary artery disease/chronic heart failure patients with and without low glomerular filtration rate

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Response letter

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate the reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "Relationship between drug application and mortality rate in Chinese older coronary artery disease/chronic heart failure patients with and without chronic kidney disease".

Those comments and suggestions are all valuable and very helpful for us to revise and improve our paper, as well as very important to direct our researches. We study the reviewer’s comments carefully and try our best to revise the paper. Attached please find the revised version, which we would like to submit for your kind consideration.

Reviewer 1:

1. Thank you for submitting this interesting article. Please consider the following comments:

Major Points: Please note the Ethical policy of the journal "Research involving human subjects, human material, or human data, must have been performed in accordance with the Declaration of Helsinki and must have been approved by an appropriate ethics committee. A statement detailing this, including the name of the ethics committee and the reference number where appropriate, must appear in all manuscripts reporting such research. If a study has been granted an exemption from requiring ethics approval, this should also be detailed in the manuscript (including the name
of the ethics committee that granted the exemption). Further information and documentation to support this should be made available to the Editor on request. Manuscripts may be rejected if the Editor considers that the research has not been carried out within an appropriate ethical framework. In rare cases, the Editor may contact the ethics committee for further information." In the current manuscript it is not clear when written consent was obtained, and it is not stated whether the Declaration of Helsinki was followed.

We are very sorry for our unclear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in the Declaration part of our manuscript. The study was approved by Ethics Committee of Chinese People's Liberation Army General Hospital (Beijing, China; Number: 038). Written consent was obtained when admission and Helsinki declaration was followed by the study.

2. Please clarify which specifically named drugs were included in each of the classes you investigated.

We are very sorry for our unclear description. Thank you for your useful suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in our manuscript. Aspirin, clopidogrel, beta-blockers, such as metoprolol, atenolol and bisoprolol, CCBs, such as nifedipine, amlodipine and felodipine, nitrates, such as sosorbide dinitrate and isosorbide mononitrate, ACEI/ARBs, such as captopril, enalapril, benazepril, fosinopril, losartan, valsartan and irbesartan, statins, such as simvastatin, pravastatin, atorvastatin and rosuvastatin, and digoxin were recorded in the database.

3. Please provide a greater narrative description regarding Table 2, 3 and 4. At present, it is not clear what each of the columns of p values refers to.

We are very sorry for our unclear description. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we provided greater narrative description regarding Table 2, 3 and 4 in our manuscript.

4. Please rewrite your discussion to include commentary on 1) comparison of your results with those of RCTs 2) Discussion of relevant clinical guidelines in light of your work 3) Weaknesses of your work - in particular the potential for confounding by indication. Please make clear that any findings would need to be replicated in RCTs if they were to be used in clinical decision making.

We are very sorry for our unclear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in our manuscript. Anti-platelet drugs have been recommended as fundamental treatment for CAD by ACC/AHA guidelines. The
Hypertension Optimal Treatment (HOT) study has shown that aspirin more significantly reduced major cardiovascular events and mortality rate in patients with renal function decline than those with normal renal function. Beta-blockers have been found to improve clinical symptoms in randomized controlled trials (RCTs) and considered as chronic therapy for CAD by ACC/AHA guidelines. Meanwhile, beta-blockers have been suggested to reduce the risk of HF death in RCTs and recommended to treat stable and symptomatic HF by ACC/AHA/ESC guidelines. However, due to adverse effects including possible hypotension and conflicting outcome, beta-blockers have been underused by clinical doctors in patients with renal function decline. CCBs and nitrates have been realized to improve clinical symptoms in RCTs and recommend to treat CAD intolerable to beta-blockers by ACC/AHA guidelines. Nitrates have the potential to reduce death risk in RCTs and recommended as a supplement to treat symptomatic HF with or intolerable to ACEI/ARBs by ACC/AHA/ESC guidelines. ACEI/ARBs have been demonstrated to reduce mortality rates in RCTs and recommended to treat CAD and HF by ACC/AHA/ESC guidelines. Even though with this evidence-based consensus of cardiovascular and renal protection with ACEI/ARBs, there are still many experts worrying that hypotension, hyperkalemia and renal function decline are ominous signs of poor outcome, especially in older patients with low GFR levels. Statins have the potential to play significant role in cardiovascular protection in both patients with and without renal function decline. Statins have been recommended as conventional treatment for CAD by ACC/AHA guidelines. Digoxin has been recognized to improve clinical symptoms in RCTs and recommended as a supplement to treat symptomatic HF by ACC/AHA/ESC guidelines. This analysis had one limitation. Patients had a median age of 86 years and relatively shorter survival time than younger patients in this analysis. Potential period over which drugs reduce mortality rates might not be reached in these patients. Thus, its results might not be simply generalized to younger patients.

5. Minor Points: Please ensure that the entire manuscript is proof-read by a fluent English Speaker.

We are very sorry for our unclear description. Thank you for your useful suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we sought the help of an American expert to modify our manuscript.

6. Please describe CKD as a 'common' rather than a 'popular' disease.

We are very sorry for our unclear description. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we replaced popular with common in our manuscript.

Reviewer 2:

1. Thank you for submitting your paper to BMC Pharmacology and Toxicology. It was a very interesting a pleasurable read. Below you will find some comments I have regarding the paper:
As the definition of CKD mentioned in your paper included only those patients with a GFR < 60 mL/min/1.73, it is important to note that KDOQI guidelines further define CKD as "kidney damage for 3+ months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR..." This includes patients with GFR > 90 (Stage 1 CKD), and GFR 60-89 (Stage 2 CKD). Therefore, generalizing conclusions to all CKD patients may be inappropriate.

We are very sorry for our unclear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we replaced CKD with GFR<60ml/min/1.73m2 in our manuscript.

2. Average survival of an 85-year old adult with a GFR of 47.2 (your cohort's average) is around 2.5 years for both males and females, and it is likely lower in patients with comorbid CHF and/or CAD. In contrast, a 75-year old male and female patient with similar GFR can expect to live 6.2 and 7.9 years, respectively. For reference, in the general population an 85 year old man can expect to live another 7.9 years, and woman 5.8 years. (Neild 2017, PMID: 27115888). As such, the latency period over which statins, for example, reduce mortality may not be reached in this patient cohort. As with point 1, generalizability to younger patient populations may be an issue regarding your study's conclusions. Your paper does specify "older patients". However, the abstract says patients aged 60 or older were included but average age in your cohort is 85 with an interquartile range of 81 - 89. I feel it may be easier to read your paper in context if you specify the aforementioned both in materials AND as a part of your conclusion, as opposed to saying "older" patients.

We are very sorry for our unclear description. Thank you for your useful suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in the discussion and conclusion of our manuscript. This analysis had one limitation. Patients had a median age of 86 years and relatively shorter survival time than younger patients in this analysis. Potential period over which drugs reduce mortality rates might not be reached in these patients. Thus, its results might not be simply generalized to younger patients. The following conclusions were drawn in this analysis of patients with a median age of 86 years.

3. Your study found that antiplatelet therapy did not lead to improved survival in patients with CAD and comorbid CKD. Could this be partly explained by the uremic-induced platelet dysfunction inherently seen in patients with CKD? If yes, I feel it may be useful to briefly discuss this in your paper's 'discussion' section.

We are very sorry for our unclear description. Thank you for your kind suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we made the corresponding modification in our manuscript.
4. I feel that it may be useful in aiding reader comprehension and flow to have the paper re-edited for grammar and syntax. I hope these will be useful to you in revising this paper, and I wish you the best of luck in its publication.

We are very sorry for our unclear description. Thank you for your valuable suggestion very much. Your valuable suggestions are very valuable and helpful for us to improve our paper. Under your guidance, we sought the help of an American expert to modify our manuscript.

We have to apologize for giving you so many troubles. We deeply appreciate your consideration and suggestions of our manuscript and look forward to receiving your comments. Your comments and suggestions give us not only great help in revising the article, but also significant revelation in our scientific research. Your kind guidance is our good luck. We wonder if the modification could meet your requirements. If you have any queries, please don’t hesitate to contact us.

Thank you and best regards.