Author’s response to reviews

Title: Increased risk of aspirin-induced gastric mucosal erosion in elderly Chinese men harboring SLCO1B1*1b/*1b while using aspirin and an ACEI or ARB concomitantly

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Dear editors and Reviewers:

We thank the helpful comments and have revised the manuscript accordingly. According the comments I deleted the data of women patients and the part of clopidogrel because the sizes of them were too small and I decided to collect data continually for research in the future. This article retained the part of aspirin and SLCO1B1 finally.

The following is my answer to the problems.

1. I have edited the language by using Liwen professional language editing service.

2. I have fully amended the abbreviations and references following the rules of journal. I also move out Chinese punctuation marks everywhere carefully.

Please further analyze potential effects of gene-gene or allele-allele interactions on the gastric muscular injury when patients took the medicine.

3. The wild type of SLCO1B1 is *1a/*1a (AA/TT 388A and 521T). The subjects who have 388G allele (A mutate into G) have higher activity of OATP1B1 protein transport which means drug blood concentrations is lower. In contrast, people who have wild allele 521T have higher activity of OATP1B1 protein transport than 521C allele subjects. So our study suggest the subjects who have SLCO1B1*1b/*1b (GG/TT 388G and 521T) have highest activity of OATP1B1 protein transport than
other subjets, hinting that drug blood concentrations may be lowest in *1b/*1b subjects.

How to link the appearance of aspirin-induced gastric muscular erosion to the presence of these SNP tested in the aspirin group? Why the author claims that SLCO1B1 SNPs were more associated with the risk of patient taking Aspirin? 4. Our study believes people who have aspirin-induced gastric muscular erosion partly because these subjects lost the effect of protection of ACEI and ARB. The subjects who have SLCO1B1*1b/*1b can reduce the blood concentration of ACEI and ARB which diminish these drugs’ protective effect for stomach.

Please double check the conclusions presented in ref. 22. 5. The the conclusions presented in ref. 22 is “Mwinyi et al. suggested that the activities of OATP1B1 protein transport in *1b/*1b (GG/TT 388G and 521T) subjects was significantly higher than *1a/*1a (AA/TT) subjects in vivo, hinting that drug blood concentrations may be lower in *1b/*1b subjects.” In the revised article the ref. 22 converted into ref. 23.

The work had screened 365 patients. And 268 patients had been taking aspirin, 97 patients had been taking clopidogrel. To be frank, the size of control population in each group for determining the SNP ratio is rather small. And the author described that there were only 11 women patients in the whole population. Then the result of this work is mainly based on male patient data. There may be sexual discrepancy on those SNP which had not been found in the study. 6. Because the women are rare in our cohorts I delete the women patients in case of avoiding sexual discrepancy and add the men patients. Meanwhile I have modified the name of the article in accordance with the content.

I am very confusing about the ratio of SLCO1B1 SNP in the group of patients. 7. Allele of 388/521 is not meaning the ratio of SLCO1B1 SNP, its real meaning represents the combination of the allele.

What does the P values mean in the allele frequencies for HWE 8. As the most important principle in population genetics, Hardy-Weinberg equilibrium (HWE) is a rule to check whether observed genotypic frequencies and allele frequencies between parents and their off-spring are in equilibrium in a population.

The author had described several other relevant factors. Why and how those factors had been considered to be investigated? 9. Several other relevant factors for example age, history of gastric ulcer, eGFR decline and so on are consistent with other article summarizing the GI bleeding risk factors in aspirin users presented in ref. 12.

Does it help for the future therapies or not? 10. Finally our study found that the SLCO1B1*1b/*1b homozygote may be a useful genetic predictor for aspirin-induced gastric mucosal erosion in senior Chinese male patients also taking ACEIs or ARBs.