Author's response to reviews

Title: Association between -T786C NOS3 polymorphism and resistant hypertension: A prospective cohort study

Authors:

Ignacio Cruz-Gonzalez (cruzgonzalez.ignacio@gmail.com)
Esther Corral (verkoop8@hotmail.com)
Maria Sanchez-Ledesma (mariasanchezledesma@hotmail.com)
Angel Sanchez-Rodriguez (asanro@usal.es)
Candido Martin-Luengo (cmluengo@usal.es)
Rogelio Gonzalez-Sarmiento (gonzalez@usal.es)

Version: 3 Date: 11 June 2009

Author's response to reviews:

Ref.: 6196910552537879 BMC cardiovascular disorders

Association between -T786C NOS3 polymorphism and resistant hypertension: A prospective cohort study

6-June-09

Dear Editor of BMC Cardiovascular Disorders,

We have addressed the constructive and helpful comments of your reviewers below and modified the paper according. We believe that with your help the manuscript is much improved and hope that you find it suitable for publication on this occasion.

Yours sincerely,

Ignacio Cruz-Gonzalez, MD, PhD
Division of Cardiology
University Hospital of Salamanca

Rogelio Gonzalez Sarmiento
Cancer Research Center (CIC)
University of Salamanca
Reviewers’ comments:

Reviewer #1:
1) eNOS genotypes and alleles frequencies in healthy subjects were not described. If the authors don’t have these data, remove the clinical data from table 1 and include in the discussion other articles citing the eNOS frequencies in Spanish population. If you have these frequencies, put them in table 2 e 3.

• We have already included the data of eNOS genotypes and alleles frequencies in healthy subjects in our previous revision of the manuscript according to the reviewer’s suggestion (Results section, first paragraph of “Distribution of the 894G>T genotypes” and first paragraph of “Distribution of the –786T>C genotypes”). We consider that if we put that data in tables 2 and 3, the tables will be more complicated to understand. Anyway if you considered that we should put them in tables 2 and 3 we will do that.

2) In table 1 information about SBP, DBP and BMI, must be include

• We have included BMI, SBP and DBP in table 1.

Moreover, if you decided maintain data of retinopathy, DM (type 1 or 2) and left ventricle hypertrophy you must to discuss a possible association of the Glu298Asp polymorphism with this pathologies besides resistant hypertension.

• We have included a new paragraph in the discussion section.

Reviewer#2.
• No modifications or revisions are suggested.

Reviewer#3

Major Compulsory Revisions
1. In this study, a clinical definition of resistant hypertension is used which involves excluding those subjects with: a.) secondary causes of hypertension; b.) white coat hypertension; c.) inadequate dosing of antihypertensive medications; and d.) non-adherence to treatment. Detailed information regarding how subjects were included or excluded in the study, for at least each of these factors, must be delineated. Protocols and validation of measures such as analytic control and
adherence tests should be included. What types of diets were subjects ingesting during the period of observation? Were dietary influences controlled during the period of blood pressure assessment? Pertaining to the assessment of target organ damage, were funduscopy and echocardiography measures validated? - The authors note that the specific data are not available but should describe the process nevertheless, e.g. the presence of secondary hypertension determined on clinical grounds.

• We have described the process in the methods section

The authors’ responses regarding funduscopy and echocardiography should be included in the manuscript.

• We have included a new sentence in the methods section according to the suggestion.

2. A table of all baseline characteristics including statistical comparison between the resistant hypertensive and control groups should be included. This table should include several relevant factors such as body mass index or other suitable anthropometric values and lipid values. Likewise a table of antihypertensive medication use between groups would be useful. Results of the 24-hour ambulatory blood pressure assessment were not included. Details of the multivariate analysis should be included. Were multiple models investigated? The issue and handling of multiple comparisons should be explicitly specified in the methods section. It would appear that no correction of p-values for multiple comparisons was applied in this study. - The suggestion of including body mass index was ignored. Such a factor is needed for comparison between groups and in the multivariate analyses.

• We have included the body mass index according to the suggestion.

- Regarding the multiple comparisons issue, a more detailed explanation as to why this was not done should be included in the manuscript itself.

• We have explicitly included this comment in the limitations section, and also we have stated that this cohort has been used in other study

3. Acknowledgment of limitations should be explicitly included. This cohort has possibly been used other studies (J Hum Hypertens. 2009 Mar 12 - epub ahead of print) which would also have an effect on the multiple comparisons issue as noted above. This issue should be addressed.

- No response was provided as to whether this cohort was used in other studies.

• We have explicitly included this comment in the limitations section

Minor Essential Revisions
1. Several grammatical errors are still present. On page 4, “Once excluded the secondary causes of hypertension and those patients who did not adhere [to] lifestyle measures…”.

- The manuscript has been reviewed again, grammatical errors have been fixed.

Discretionary Revisions

1. To provide additional perspective, the discussion would benefit from a brief synopsis of the studies of these particular polymorphisms and other nitric oxide synthase variants with respect to hypertension including references to positive, negative, and indeterminate studies.

2. Was there consideration of a haplotype analysis in any fashion?

   The discussion section has been improved overall.

- No further modifications or revisions are suggested.

Reviewer #4

The authors added comments and specific responses to the criticisms that were raised. The manuscript is now acceptable for publication.

- No modifications or revisions are suggested.