Author's response to reviews

Title: T/L-type calcium channel blocker reduces composite ranking for relative risk according to new KDIGO guidelines in patients with chronic kidney disease

Authors:

Masanori Abe (abe.masanori@nihon-u.ac.jp)
Kazuyoshi Okada (kokada@med.nihon-u.ac.jp)
Hiroko Suzuki (suzuki.hiroko46@nihon-u.ac.jp)
Yoshinori Yoshida (yoshida.yoshinori@nihon-u.ac.jp)
Masayoshi Soma (souma.masayoshi@nihon-u.ac.jp)

Version: 2 Date: 15 February 2013

Author's response to reviews: see over
February 15, 2013

Editor-in-Chief
BMC Nephrology

Dear Sir,

Thank you for your letter dated January 28, 2013. We are pleased to know that our manuscript was rated as potentially acceptable for publication in *BMC Nephrology*, subject to adequate revision and response to the comments raised by the reviewers.

Enclosed please find a revised manuscript entitled, “T/L-type calcium channel blocker reduces the composite ranking of relative risk according to new KDIGO guidelines in patients with chronic kidney disease”, by Abe et al., which we wish to submit for publication in *BMC Nephrology*. Your kind consideration of this paper would be greatly appreciated. I look forward to hearing from you.

Sincerely yours,

Masanori Abe, M.D. PhD,
Division of Nephrology, Hypertension and Endocrinology,
Department of Internal Medicine,
Nihon University School of Medicine,
30-1, Oyaguchi Kami-chou, Itabashi-ku,
173-8610, Tokyo,
Japan
Tel.: +81-3-3972-8111
Fax: +81-3-3972-8311
E-mail: abe.masanori@nihon-u.ac.jp
Comments to the reviewers

We thank the Editor and the Reviewers for providing insightful feedback, which has helped us to improve our paper.

Reviewer's report

**Title:** T/L-type calcium channel blocker reduces composite ranking for relative risk according to new KDIGO guidelines in patients with chronic kidney disease

**Version:** 1 **Date:** 15 January 2013

**Reviewer:** Jicheng Lv

**Reviewer's report:**

This is a randomized clinical trial with short follow-up which evaluate the effect of T/L-type calcium channel blocker on the kidney protection in patients with chronic kidney disease. The findings are interesting that benidipine significantly reduced the albuminuria, and also relative risk ranking of CKD classification as compared to amlodipine.

**Major points**

1) The strength of this study is its randomized controlled design, and the major limitation is the short follow-up and use surrogate endpoints and its not pre specified outcomes. The authors should clearly addressed it in the discussion section. As described in one report from National Kidney Foundation and the US Food and Drug Administration [AJKD 2009;54(2):205], microalbuminuria is not good surrogate for ESKD. This also shown in the ONTARGET and
ACCOMPLISH or ATTITUDE trials.

Thank you for your suggestions. We agree with your comments and have added the major limitation of our study to the Discussion section.

“Despite the findings, our study was limited by the relatively small sample size and the short period of treatment. Moreover, the changes in sCr levels were too small for adequate evaluation of the influence of CCB therapy. It has been reported that there is insufficient evidence to assume that a reduction in albuminuria levels will lead to an improvement in clinical outcomes such as progression to ESRD, a CVD event, or death [43]. Additional studies are therefore necessary to more firmly establish the validity of changes in albuminuria as a surrogate for kidney disease progression. Furthermore, long-term investigations are also necessary to accurately assess the preventive renal and cardiovascular effects of benidipine therapy in patients with CKD. Moreover, to assess the changes in risk categories of the KDIGO classification that precisely reflect prognosis, requirements for renal replacement therapy and other renal or cardiovascular events should be considered endpoints.”

2) The mechanism of benidipine reducing albuminuria comes its dynamics of lowering the Glomerular pressure and will also reduce the GFR in the short term follow-up. I’m surprised for its effect of increased the GFR. The authors should demonstrate the sequential GFR changing from 1st to 6th month in figure

Thank you for your suggestion. We have added the sequential GFR changes from baseline to 6 months as shown in Figure 2.

3) All the patients that have received radiation should be included the final
Thank you for your suggestion. However, none of the patients received radiation.

Minor points

1) The authors have described the process for randomization, but it’s still not clear for the randomization concealment.

Thank you for your suggestion. We have altered the description concerning the randomization method as follows:

“Subjects were randomly assigned to two groups prior to the start of the study. Dynamic balancing randomization was carried out based on age, gender, serum Cr (sCr) levels and the urinary albumin/Cr ratio measured at the time of registration, and the presence or absence of diabetic nephropathy. An independent investigator with no previous knowledge of the subjects before commencement of the trial, monitored randomization of the order of entry of the subjects. The details of the assignment were then given to four independent investigators.”

2) Regarding the estimated GFR formula, why the authors not using the CKD-EPI?

Thank you for your suggestion. This was also referred to by another reviewer, and thus the following was provided in the Discussion section.

“Although the risk categories in the KDIGO guidelines were formed using pooled outcome data from numerous populations through application of the Modification of Diet in Renal Disease (MDRD) Study equation, it has been reported that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation more accurately...
estimates GFR using the same variables, especially at higher GFR [39]. The CKD-EPI equation is a better predictor of risk than the MDRD Study equation in CKD cohorts as well as in cohorts with higher eGFR [39]. However, CKD-EPI equations were developed in mostly Caucasian and African American populations. A previous study revealed that eGFR values obtained using CKD-EPI equations with sCr were significantly higher than the actual GFR in Japanese subjects [40]. Moreover, when the bias, precision and accuracy of the GFR equations were compared in Japanese subjects stratified by measured GFR, Japanese GFR equations performed well in those with a GFR < 60 mL/min/1.73 m² compared with the coefficient-modified CKD-EPI equations [40]. Furthermore, in a study using Japanese GFR equation, reduced eGFR was independently associated with incident CVD events in Japanese patients with type-2 diabetic nephropathy and patients with non-diabetic CKD [41,42]. In the present study, since the mean eGFR at baseline was 44.6 ± 1.9 mL/min/1.73 m², we assessed the changes in eGFR using the Japanese GFR equation.”

3) In table 1, the authors should provide the p-value

Thank you for your suggestion. P-values have been provided in Table 1.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer's report

Title: T/L-type calcium channel blocker reduces composite ranking for relative risk according to new KDIGO guidelines in patients with chronic kidney disease

Version: 1 Date: 28 August 2012

Reviewer: Chagriya Kitiyakara

Reviewer's report:

Major compulsory revisions:

1) Provide data on calibration methods, coefficient of variation of the serum creatinine

Thank you for your suggestion. We have added the following to the Methods section.

“Serum samples were assayed for Cr in a central laboratory (Central Laboratory; SRL Co, Tokyo, Japan) by means of the enzymatic Cr assay method using a Japan electron Cr auto-analyzer, model JCA-BM8060 (JEOL Ltd., Tokyo, Japan) and enzyme solution (Preauto-S CRE-L; Sekisui Medical Co., Ltd., Tokyo, Japan). The sCr values obtained in the central laboratory were compared with the standard reference material (SRM914a, The National Institute of Standards and Technology, Gaithersburg, USA) by using a calibration panel of 50 samples.”

2) The authors used the Japanese equation to estimate GFR. There is an uncertainty which equation should be used in Asian populations. While the Japanese equation may be appropriate for the population under study, the KDOQI guidelines risk categories were formed using pooled outcome data from
many populations (including Asians) using the MDRD equation

i) The authors should address the issues of using the Japanese equation on risk assessment/categorization as compared to MDRD or CKD-EPI.

Thank you for your suggestion. We agree with your comments and have accordingly addressed the issue of comparing the Japanese equation and MDRD or CKD-EPI equation in the Discussion section as follows:

“Although the risk categories in the KDIGO guidelines were formed using pooled outcome data from numerous populations through application of the Modification of Diet in Renal Disease (MDRD) Study equation, it has been reported that the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation more accurately estimates GFR using the same variables, especially at higher GFR [39]. The CKD-EPI equation is a better predictor of risk than the MDRD Study equation in CKD cohorts as well as in cohorts with higher eGFR [39]. However, CKD-EPI equations were developed in mostly Caucasian and African American populations. A previous study revealed that eGFR values obtained using CKD-EPI equations with sCr were significantly higher than the actual GFR in Japanese subjects [40]. Moreover, when the bias, precision and accuracy of the GFR equations were compared in Japanese subjects stratified by measured GFR, Japanese GFR equations performed well in those with a GFR < 60 mL/min/1.73 m² compared with coefficient-modified CKD-EPI equations [40]. Furthermore, in a study using the Japanese GFR equation, reduced eGFR was independently associated with incident CVD events in Japanese patients with type-2 diabetic nephropathy and patients with non-diabetic CKD [41,42]. In the present study, since the mean eGFR at baseline was 44.6 ± 1.9 mL/min/1.73 m², we assessed the changes in eGFR using the Japanese GFR equation.”
ii) The authors should provide references to show that risks of outcome is associated with different CKD stage using the Japanese equation.

Thank you for your suggestion. We have added references 41 and 42.


iii) It would be interesting to evaluate the changes in risk categories using MDRD or CKD-EPI in addition to the Japanese equation.

Thank you for your suggestion. In Japan, all patients are assessed using the Japanese GFR equation, as also recommended by the Japanese Society of Nephrology, because this equation is more accurate than the MDRD and CKD-EPI equations in Japanese populations. The following explanation has been added to the Methods section.

“Glomerular filtration rate was estimated using the modified final recommendation equation for Japanese patients of the Japanese Society of Nephrology-CKD Initiatives (JSN-CKDI), since eGFR values obtained using this method are more accurate for Japanese patients with CKD [16].”

3. The data used for KDIGO risk categorization were mainly derived from baseline data.
- The authors should discuss the studies that showed that changes in risk after treatment is associated with good outcome (e.g. post-hoc IDNT and others) as well as other studies (if available) that shows that changes in risk categories increases/decreases outcome risk.

Thank you for your suggestion. Accordingly, we have added the following to the Discussion section.

“It has also been reported in post-hoc analysis of RENAAL and IDNT trials that a dual approach targeting both blood pressure and albuminuria is important in improving cardiovascular outcomes [20]. Furthermore, post-hoc analysis of the IDNT trial using eGFR as the principal outcome measure, confirmed that ARB irbesartan significantly slows the long-term rate of decline in eGFR, resulting in delayed progression towards ESRD by at least 33%. This finding was explained by reductions in BP and proteinuria [21].”

4) The authors postulated that the improvement in GFR in the benipine group might be due to improvement in albuminuria.

- It would be interesting to assess correlation of changes in albumin and GFR in these patients.

Thank you for your suggestion. We have added results of the correlation between the changes in albuminuria and GFR. Since eGFR values in the benidipine group were unchanged in many subjects, we believe there was no significant correlation between albuminuria and eGFR changes.

“There was no significant correlation between the changes in albuminuria and eGFR in either group (amlodipine group: r = 0.081, P = 0.575, benidipine group: r = -0.127, P =
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests