Author's reply

We are grateful for the opportunity to respond to Dr. Kawada's letter, in which he raised two points about our article published in the *Journal of Cardiology* in 2013, "Prognostic value of B-type natriuretic peptide and its amino-terminal proBNP fragment for cardiovascular events with stratification by renal function".

In this article, we evaluated the utility of B-type natriuretic peptide (BNP) and its amino-terminal proBNP fragment (NT-proBNP) as predictors for mortality and cardiovascular events in patients with renal dysfunction. We also determined equations defining NT-proBNP levels as a function of BNP levels for patients with different stages of chronic kidney disease (CKD), because of a lack of an equation. BNP and NT-proBNP are important biomarkers for the diagnosis and assessment of severity of cardiac failure and for predicting the prognosis of the affected patients. The biologically active BNP and its inactive counterpart, NT-proBNP, are produced by proteolytic digestion of the common precursor hormone proBNP. So the same molar BNP and NT-proBNP are produced biochemically. However, these molecules show different blood concentration profiles, owing to the difference in standard peptides used in each assay system, metabolic patterns, and patients' renal function. Comparison of the predictive performance of these biomarkers and the quantitative relationship between their blood levels are topics of ongoing debate.

The first point of Dr. Kawada's comments relates to the areas under the receiver operating characteristic curves (AUC) for all-cause deaths and the composite end point. In particular, he suggested testing the superiority of NT-proBNP using specific software programs. In our study, NT-proBNP and BNP yielded similar AUC for patients with CKD stages 1–3. In patients with CKD stages 4 and 5, NT-proBNP provided larger AUCs than BNP, but the difference was not statistically significant when tested using a method described in the literature [1]. For this reason, we observed that "NT-proBNP *may be* superior to BNP in patients with an eGFR <30 ml/min/1.73 m^2". Our definite conclusion is that both BNP and NT-proBNP are useful biomarkers for all-cause mortality and cardiovascular events. It would be unfortunate if our expression was taken to be more definitive than was intended.

Second, based on the observed close correlation between NT-proBNP and BNP, Dr. Kawada suggested that the multivariate analysis of the correlation between clinical parameters and NT-proBNP should exclude BNP from explanatory variables and, likewise, the multivariate analysis of the correlation between clinical parameters and BNP should exclude NT-proBNP from explanatory variables. It is correct that NT-proBNP and BNP levels were significantly correlated, as illustrated in Fig. 1 of our article. Therefore, multivariate correlation analyses of NT-proBNP excluded BNP from explanatory parameters in our report, and vice versa. Readers may follow our procedure if they carefully examine Tables 3 and 4, in which neither NT-proBNP nor BNP is included in the lists of explanatory variables. We reject Dr. Kawada's remark as a misunderstanding on his part. The equations in the article that defined NT-proBNP levels as a function of BNP must logically include both parameters.

We believe that our response fully addresses Dr. Kawada's concerns. We are pleased that our article drew the attention of the medical community and stimulated further discussion.

Reference

[1] Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983;148:839–43.

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