Concerns for the Heart Failure Reduction in the NAGOYA HEART Study Based on Meta-Regression From the Evidence

To the Editor:

The NAGOYA HEART Study\(^1\) compared the efficacies of an angiotensin II type 1 receptor blocker (ARB) valsartan and a calcium channel blocker amlopidine on cardiovascular morbidity and mortality as a primary outcome in Japanese hypertensive patients with glucose intolerance. Time-to-event curves for primary outcomes did not significantly differ between the 2 groups (hazard ratio, 0.97; 95% confidence interval [CI], 0.66–1.40; \(P=0.85\)). Despite no significant differences in the risk of myocardial infarction, stroke, coronary revascularization, or sudden cardiac death between the 2 groups, the differences in the risk of myocardial infarction, stroke, coronary revascularization, or sudden cardiac death between the 2 groups, the incidence of admission because of heart failure was significantly less in the valsartan group than that in the amlopidine group (hazard ratio, 0.20; 95% CI, 0.06–0.69; \(P=0.0012\)). It seems strange, however, that the achieved blood pressure (BP) between the 2 groups is almost the same (131/73 mm Hg in the valsartan group and 132/74 mm Hg in the amlopidine group at 54 months). Herein, we would like to assess the specificity of the significant relative risk reduction for heart failure with the achieved systolic BP (SBP) difference of only –1 mm Hg shown in the NAGOYA HEART Study by means of a novel meta-regression analysis of a data set included in the most robust evidence\(^2\) for BP-lowering treatment with agents inhibiting the renin–angiotensin system.

In a study by the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC),\(^2\) there were 17 angiotensin-converting enzyme inhibitor trials (\(n=101626\)), 9 ARB trials (\(n=45212\)), and 3 direct head-to-head trials (\(n=18477\)). We selected 11 comparisons from 10 of the 12 ARB trials (including 3 direct head-to-head trials) in the NAGOYA HEART Study by means of a novel meta-regression analysis of a data set included in the most robust evidence\(^2\) for BP-lowering treatment with agents inhibiting the renin–angiotensin system. In the NAGOYA HEART Study,\(^1\) the similar significant relative risk reduction for heart failure with the achieved SBP difference of nearly zero shown in the NAGOYA HEART Study, which is irreconcilable with the result of the present meta-regression analysis of the data set included in the most robust evidence.\(^2\)

With respect to Japanese valsartan trials, the Jikei Heart Study\(^3\) and KYOTO HEART Study,\(^4\) several concerns have arisen.\(^5–7\) Kyoto Prefectural University of Medicine announced on July 11, 2013, that the data used in the KYOTO HEART Study were manipulated, and manipulation of data is suspected because the research team had a tendency to report fewer incidents of disease in the valsartan group and more incidents of disease in the non-ARB group.\(^8\) Late December 2012, ex-professor Matsubara requested that his papers for the KYOTO HEART Study be withdrawn because of data problems after the data in his study were questioned.\(^9\) In the end of July 2013, an interim report by a Jikei investigation committee said that a large part of the BP data on the Jikei Heart Study paper differed from data on medical records.\(^10\) Professor Mochizuki, who led the Jikei Heart Study, is offering to withdraw his paper\(^1\) published in The Lancet, noting grave doubts have emerged about the credibility of the research. What is common in these 2 Japanese valsartan trials\(^3,4\) is the significant relative risk reduction for cardiovascular outcomes (angina pectoris,\(^3,4\) stroke,\(^3,4\) and heart failure\(^1\)) without the achieved SBP difference. Also in the NAGOYA HEART Study,\(^1\) the similar significant relative risk reduction for heart failure without the achieved SBP difference has been reported.

**Figure.** Associations of blood pressure reduction with risk reduction for heart failure in trials of angiotensin II type 1 receptor blockers. Open circles represent trials included in the study by the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC),\(^2\) and a closed circle represents the NAGOYA HEART Study,\(^1\) with the area of each circle inversely proportional to the variance of the log odds ratio. A fitted line with curves represents the summary meta-regression measure with lower and upper limits of its 95% confidence interval for the trials included in the BPLTTC study (not including the NAGOYA HEART Study).

### Disclosures

None.

Hisato Takagi
Takuya Umemoto
for the All-Literature Investigation of Cardiovascular Evidence (ALICE) Group
Department of Cardiovascular Surgery
Shizuoka Medical Center
Shizuoka, Japan

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Hisato Takagi and Takuya Umemoto
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