To the Editor:

With interest we read the article by Dr Kojima et al evaluating whether the effect of azelnidipine on coronary plaque volume (PV) would not be inferior to that of amlodipine assessed by intravascular ultrasound (IVUS). The authors showed a significant regression of $-4.67\%$ and $-4.85\%$ of the percent change in PV (the primary endpoint) in the azelnidipine and amlodipine groups, respectively. The upper limit of the 95% confidence interval of the difference in the mean percent change in PV between the 2 groups ($0.18\%$, $-4.62$ to $4.98\%$) did not exceed the predefined non-inferiority margin of $6.5\%$. Then, the authors concluded that “azelnidipine was not inferior to amlodipine for primary efficacy. In addition to standard medical therapy, dihydropyridine CCBs will retard PV progression in hypertensive patients”. We raise several concerns about the study’s design.

First, although the authors used a non-inferiority study design, the primary endpoint (ie, the percent change in PV) was examined only in $58\%$ ($115/199$) of randomized patients. Finding no difference is usually the desired outcome in non-inferiority trials and is favored by studies with many dropouts and missing data. Given the many dropouts and missing data in previous studies using IVUS variables, it seems inappropriate to use IVUS variables as a primary endpoint in non-inferiority trials.

Second, although the authors used amlodipine as the active control, no previous studies have proven the efficacy of amlodipine over placebo using IVUS variables. An IVUS substudy showed only a trend toward less progression of atherosclerosis in the amlodipine group vs. placebo (change of percent atheroma volume: $0.5$ (3.9) vs. $1.3$ (4.4); $P=0.12$).\(^5\) Moreover, there were several differences in important design features (primary variables, IVUS analysis, dose/duration of treatment, population) between the previous superiority trial\(^5\) and the current trial that violate the assumptions (constancy and assay sensitivity).\(^7\)

Taken together, it remains unknown whether azelnidipine could retard PV progression in hypertensive patients compared with placebo/control.

References


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