We would like to thank Dr. Ma et al. of their letters for their interest in our paper and comments on our findings. We do not disagree with their opinions regarding the many dropouts and missing data in the current trial. We understood this limitation, and described it in our report. Among 84 non-intravascular ultrasound (IVUS)-completing patients, 46 were lost to follow up, 13 withdrew consent, 15 did not undergo IVUS examination, and there was poor image quality of follow-up IVUS in 10 patients. Therefore, a total of 115 patients had evaluable IVUS at both baseline and follow-up. Although our analysis of IVUS parameter was based on 115 patients, recalculation of the actual statistical power for the primary endpoint, indicated sufficient power still remained because the variability of the % change of plaque volume (PV) was narrower than what we expected at the start-up of this trial.

Regarding the second point, we agree that no previous studies have proven the efficacy of amlodipine over placebo using IVUS variables. As the reviewers pointed out, the NORMALIZE study demonstrated that comparison of amlodipine with placebo showed a trend toward statistical significance (P=0.12). However, in the subgroup with baseline blood pressures above the mean, significant reduction in progression was observed in the amlodipine group compared with placebo (P=0.02). Furthermore, paired analysis of each regimen compared with baseline revealed progression in the placebo group (P<0.001) and no progression in either the amlodipine or enalapril treatment group. Based on this data, amlodipine was effective in plaque retardation compared with placebo in patients in the higher blood pressure group. The backgrounds of the patients in the NORMALIZE sub-study were similar to those of the patients in the current ALPS-J study. We believe that the most important conclusion of our work is that studies conducted in hypertensive patients.

There are several differences between our study and the NORMALIZE study in the observed plaque length and observation period. Single plaque in the percutaneous coronary intervention target vessel was observed in our trial whereas pan-coronary PV was evaluated in NORMALIZE study. Changes of PV were more exaggerated in single plaque of our study compared with pan-coronary plaque of the NORMALIZE study. Previous IVUS studies suggested that Japanese patients showed more plaque regression than American patients in conditions with the same intervention. Neither study used the most rigorous IVUS measure of atherosclerosis burden as the primary endpoint in hypertensive patients. No large-scale IVUS trials in which patients received calcium-channel blocker (CCB) have demonstrated statistically significant regression. The net efficacy of CCB in plaque change was not proved conclusively in our study because there was no placebo control group. However, drugs other than CCB were fixed and continued during the study period as a rule. Thus, CCB could have a direct impact on plaque change. Finally, larger studies may be required, using IVUS as a primary end point, to conclusively determine the efficacy of CCB on regression of atherosclerosis. We hope that our findings are investigated more fully in other analyses in future placebo-control studies.

References

Katsumi Miyauchi, MD
Hiroyuki Daida, MD
Cardiology, Department of Internal Medicine, School of Medicine Juntendo University, Tokyo, Japan

(Released online July 12, 2011)