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Robert M. Berne Cardiovascular Research Center, University of Virginia, Charlottesville, VA (K.-D.M.), USA; Department of Clinical Research and Development, National Cerebral and Cardiovascular Research Center, Suita (K.-D.M., M.K.), Japan

Mailing address: Kyung-Duk Min, MD, PhD, Robert M. Berne Cardiovascular Research Center, University of Virginia, 415 Lane Rd, PO box 801394, Charlottesville, VA 22908, USA. E-mail: km9xv@virginia.edu

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These differences are consistent with previously reported regional characteristics in Asia, as well as in Japan, and the overall characteristics of participants were comparable to those of PARADIGM-HF. As well, importantly, the characteristics of PARALLEL-HF were comparable to those of previous HFrEF trials implemented in Japan (J-EMPHASIS-HF, CHART2, JCARE-CARD), suggesting that PARALLEL-HF successfully enrolled a representative contemporary cohort of HFrEF in Japan and that the results of PARALLEL-HF infer a clinical effect of sacubitril-valsartan for HF treatment in daily practice in Japan. Also, the aforementioned regional characteristics (i.e., older age, low BMI, low blood pressure) resulted in higher MAGGIC risk scores and higher EMPHASIS-HF scores in PARALLEL-HF compared with PARADIGM-HF. Importantly, in PARADIGM-HF, a higher MAGGIC risk score or EMPHASIS-HF score was associated with larger absolute benefit from sacubitril-valsartan, implying potential benefit of sacubitril-valsartan for Japanese HFrEF patients.

It is also noteworthy that, in this article, the authors provide the clinical data after the run-in period. The run-in dose of sacubitril-valsartan 50 mg bid for 2 weeks resulted in only 2 cases of run-in failure because of adverse events while significant changes in blood pressure (121.8/72.6 to 117.5/70.4 mmHg, P < 0.01) and heart rate (73.3 to 74.9 beats/min, P < 0.01) were observed. It shows, at least, that most of the participants in PARALLEL-HF – and presumably a large number of Japanese HFrEF patients – would be able to take this new drug at the minimum dose without adverse effects and be eligible for up titration further. In PARALLEL-HF, 42% of patients in the sacubitril-valsartan arm had to reduce the dose after randomization, whereas all the participants of PARADIGM-HF took the target dose of sacubitril-valsartan 200 mg bid. Actually, in PARADIGM-HF, 42% of patients in the sacubitril-valsartan arm had to reduce the dose after randomization. Of interest, however, is that although the risk of the patients who had a dose reduction was higher than that of those who went through on the maximum dose (HR 2.5, 95% CI 2.2–2.7), the treatment benefit of sacubitril-valsartan over enalapril still remained comparable even after dose reduction (HR 0.80, 95% CI 0.70–0.93). The “residual effect” of an initial high dose could be a possible explanation. But this result may simply imply the superiority of sacubitril–valsartan over enalapril even at the lower dose. The results of PARALLEL-HF could also approach this issue.

The results of PARADIGM-HF generated the enthusiasm of cardiologists all over the world and it is believed to be the key to a new era of HF treatment. PARALLEL-HF was designed as the phase III trial to test the clinical effect of sacubitril-valsartan in HFrEF patients in Japan, but harbors huge potential to provide fundamental information for unanswered questions about the usage of sacubitril-valsartan in the real world, not limited to Japan. We shall await its results in 2019.

References