PARALLEL-HF

— A Paradigm Shift for Heart Failure Treatment in Japan? —

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Heart failure (HF) has been a leading cause of mortality for decades worldwide and a novel therapeutic strategy for HF has always been awaited. Neurohormonal peptides, namely natriuretic peptides, bradykinin and adrenomedullin, are good targets because of their favorable effects on HF through attenuating vasoconstriction and sodium retention. Neprilysin is the key enzyme responsible for the breakdown of neurohormonal peptides, so a neprilysin inhibitor would retard the pathophysiology of HF through augmentation of the benefits from neurohormonal peptides. On the other hand, however, a neprilysin inhibitor is known to provoke counteractivation of the renin-angiotensin system (RAS), presumably because of degradation of angiotensin itself. Therefore, the use of a neprilysin inhibitor requires concurrent block of the RAS. In this context, the first attempt at a neprilysin inhibitor, sacubitril, for HF treatment was made by combining an angiotensin-converting enzyme inhibitor (ACEI) inhibitor, enalapril, but it resulted in serious angioedema as an adverse effect.¹ To overcome this problem, an angiotensin-receptor neprilysin inhibitor (ARNI: sacubitril-valsartan) was designed under the name of LCZ696. In 2014, amid strong need for HF therapy, the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial showed that sacubitril-valsartan reduced 20% of mortality and hospitalization caused by HF compared with enalapril, so the study was terminated early because of the apparent benefit in the sacubitril-valsartan group.² Based on this striking result, sacubitril-valsartan was approved by both the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) under the name of Entresto® in 2015, and now it is recommended in the latest guidelines for HF from the American Heart Association and the European Society of Cardiology.

Then, based on the result of PARADIGM-HF, should we switch ACEIs or ARBs to sacubitril-valsartan in real-world clinical practice in Japan? The answer to this question has now been addressed by the Phase III prospective comparison of ARNI with ACEI to determine the novel beneficial treatment value in Japanese Heart Failure patients (PARALLEL-HF) study.³

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Although a substantial number of participants were enrolled from the Asia-Pacific region to derive conclusions about the results of PARADIGM-HF, the effect of sacubitril-valsartan in Asian HF patients is still a matter for careful discussion. The PARADIGM-HF trial analyzed 8,399 cases enrolled from many different regions of the world: 602 (7%) from North America, 1,680 (20%) from Western Europe, 2,762 (33%) from Central/Eastern Europe/Russia, 1,433 (17%) from Latin America and 1,487 (18%) from the Asia-Pacific region.⁴ However, according to the Asia-Pacific patients' data, the benefit of sacubitril-valsartan came very close to, but did not reach the statistical significance (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.69–1.04 for the primary endpoint).⁴ Also, Asian ethnicity fell short of showing a statistically significant benefit from sacubitril-valsartan (shown in the table,² indices not shown). PARADIGM-HF included patients from China, Philippines, Singapore, South Korea, Taiwan and Thailand, for the Asia-Pacific region, but not Japan. Geographic, economic and social confounders vary, even among Asian countries. Therefore, it is quite meaningful to determine the actual efficacy of sacubitril-valsartan in Japanese HF patients in PARALLEL-HF.

The patient eligibility criteria of PARALLEL-HF largely followed those of PARADIGM-HF and 225 patients with HF and reduced ejection fraction (HFrEF) were selected during the enrollment period of 2015–2016 and are still in follow-up of clinical outcomes. In this issue of the Journal, Tsutsui et al⁵ describe the baseline characteristics of the patients enrolled in PARALLEL-HF. Compared with PARADIGM-HF, the participants in PARALLEL-HF were older (67.9 vs. 63.8 years of age) and included more males (85.8% vs. 78.2%) and showed lower blood pressure (122.3/72.8 vs. 128.4/77.8 mmHg), lower body mass index (BMI: 24.5 vs. 28.1 kg/m²) and lower levels of NT-proBNP (1,130 vs. 1,612.5 pg/mL). The majority of patients in PARALLEL-HF were in NYHA Class II (93.8% vs. 64.6%). Interestingly, despite lower NT-proBNP levels and predominantly NYHA Class II participants in PARALLEL-HF, LVEF was comparable in both studies (28.1% vs. 29.5%).

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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,⁶ 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 to a higher dose. In PARALLEL-HF, participants who completed the run-in period were randomized to receive sacubitril-valsartan 100 mg bid or enalapril 5 mg bid for 4 weeks and, if tolerable, doses were up-titrated to 200 mg bid and 10 mg bid, respectively.³ The ARB component of sacubitril-valsartan 200 mg bid is equivalent to valsartan 320 mg/day, which is twice the maximum dose of valsartan in Japan. This dose was shown to be tolerable for Japanese patients with hypertension,⁷ but whether it is tolerable for Japanese HF patients remains unknown. In this context, it is important that PARALLEL-HF allowed participants to take their “tolerable maximum dose”, 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.⁸ 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.

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