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Editorial

Drug Titration for Patients With Heart Failure With Reduced Ejection Fraction Is a Challenge for Physicians in the Era of Four Pillar Drugs

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▸ See the article "Real-World Usage of Sacubitril/Valsartan in Korea: A Multi-Center, Retrospective Study" in volume 4 on page 193.

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Sacubitril-valsartan, the only clinically available medication in the angiotensin receptor-neprilysin inhibitor (ARNI) class, is now recommended as a preferred alternative to angiotensin-converting enzyme inhibitors (ACEIs) for the treatment of patients with heart failure with reduced ejection fraction (HFrEF) since the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial,[1] which demonstrated the superiority to ACEI in reducing the risk of cardiovascular and all-cause mortality and hospitalization for heart failure (HHF) in chronic HFrEF patients. The rationale for using sacubitril-valsartan in clinical practice has further been supported by studies showing the effect of sacubitril-valsartan on the reduction of the level of natriuretic peptides and improvement of clinical outcomes in patients with acute decompensated HFrEF when compared to enalapril.[2,3]

Recently updated treatment guidelines for patients with HFrEF strongly recommend using four "pillar" drugs, an ARNI or ACEI, a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 (SGLT2) inhibitor, to reduce the risk of mortality and HHF.[4,5] SGLT2 inhibitor has a single dose and does not require titration, but other three classes of four pillar medications, each agent should be started at low dose and need to be uptitrated to maximally tolerated or target dose. The sacubitril-valsartan should be titrated upward to 97 mg sacubitril and 103 mg valsartan twice daily, and the mean dose attained in the PARADIGM-HF trial was 182 mg sacubitril and 193 mg valsartan total daily, which corresponds to 93.8% of the target dose.[1] However, there are many obstacles to uptitrate medications in HFrEF patients, including low blood pressure, impaired renal function, electrolyte imbalance, and intolerance. We frequently encounter with these challenges during optimization of HFrEF medications.

According to Park et al.,[6] who reported on the current status of the use of sacubitril-valsartan for patients with chronic stable HFrEF in Korea, 4.8% of patients started with the target dose of sacubitril-valsartan at baseline and only 24.8% of patients were receiving target doses at 12 months. Surprisingly, 40% and 32% of the patients who started with doses of 24 mg sacubitril and 26 mg valsartan twice daily and 49 mg sacubitril and 51 mg valsartan twice daily, respectively, were not uptitrated to higher doses of ARNI after initiation of

sacubitril-valsartan, while 42% of patients on the low or moderate dose at baseline were gradually uptitrated. During a follow-up of 12 months, systolic blood pressure was decreased by 2.2±19.8 mmHg and the estimated glomerular filtration rate was decreased by 2.1±14.5 mL/min/1.73m^2. Although patients did not achieve target dose, the left ventricular ejection fraction was increased by 10.4±12.2%, the LV end-diastolic volume index reduced by 18.7±26.1 mL/m^2, and the N-terminal pro-brain natriuretic peptide declined at a ratio of 0.5.

Many registries or retrospective studies in patients with HFrEF have highlightened the discrepancy in the doses of HF medications between clinical trials and real-world practice. In the CHAMP-HF (Change the Management of Patients with Heart Failure) registry conducted in the United States, which included 2,588 patients with HFrEF who completed follow-up to 12 months, only 1.5% of patients were taking the stable target dose for 12 months even though participants were enrolled in the study after the U.S. Food and Drug Administration approved sacubitril-valsartan.[7] The study showed that only 0.7% of patients received all three medications at the target doses, renin-angiotensin-system blockers including ARNI, beta-blockers, and MRA at baseline and 12 months. A meta-analysis involving 16,952 European patients with HFrEF in real-world setting showed that 35% of patients achieved the target dose of ARNI.[8]

As mentioned by Park et al.,[6] the 15% of patients receiving unconventional doses less than target dose indicates physicians' concern regarding the fact that Korean patients with HFrEF are known to have low blood pressure in comparison to Western patients. However, it has been noted that the more the target dose is prescribed, the higher likelihood of LV reverse remodeling and the greater reduction in BNP compared to the sub-target dose of sacubitril/valsartan,[9,10] which will be directly associated with favorable outcomes.

As evidence from clinical trials on novel HF drugs accumulates, it is challenging to optimize HF medications to the target doses. Patient tolerance and drug-related adverse events must be closely monitored during dose titration since in most patients with HFrEF, a combination of multiple medications can result in intolerance. Achieving the target dose is linked to the maximum clinical benefit. Physicians need to overcome clinical inertia and prioritize up-titration of HF medications to maximally tolerated or target doses.

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