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Editorial

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ECG Monitoring of Reactions to Sacubitril-valsartan in Heart Failure with Reduced Ejection Fraction

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▸ See the article "Changes in QRS Duration Are Associated with a Therapeutic Response to Sacubitril–valsartan in Heart Failure with Reduced Ejection Fraction" in volume 28 on page 244.

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Conflict of Interest
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Sacubitril/valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) which is FDA-approved for the treatment of patients with chronic heart failure with reduced ejection fraction (HFrEF).[1] According to the 2016 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on New Pharmacological Therapy for Heart Failure, ACEI, ARB, or ARNI are now recommended in patients with chronic symptomatic HFrEF to reduce morbidity and mortality (class I recommendation).[2]

Neprilysin is a principal enzyme for degradation of multiple vasoactive peptides including natriuretic peptides, angiotensin, endothelin 1, adrenomedullin, opiods and amyloid-beta peptide.[3][4] Sacubitril, neprilysin inhibitor, is a prodrug that is activated to the active metabolite 'Sacubitrilat' and increases the levels of these peptides, promoting natriuresis, vasodilation and reduction of ECF volume via sodium excretion, thus eventually reducing preload and ventricular remodeling.[5] Valsartan inhibits the effects of angiotensin-II by selectively blocking the receptor type-1 (AT1), thus blockade of AT1 reduces vasoconstriction, sodium and rater retention and myocardial hypertrophy. Therefore, the cardiovascular and renal benefits of sacubitril/valsartan in HF patients are superior on cardiac fibrosis and cardiac hypertrophy than either stand-alone neprilysin inhibition or AT1 blcoker.[6][7]

PARADIGM-HF proved that sacubitril/valsartan was superior to RAAS inhibitor (enalapril), in reducing the risk of cardiovascular death by 20%, HF hospitalization by 21% and all-cause mortality by 16% and reducing overall symptoms with much better tolerability.[8-11] In the PARAMOUNT trial, sacubitril/valsartan was well tolerated with fewer serious and overall adverse events than the comparator valsartan in patients with HF with preserved EF (HFpEF, EF ≥ 45%) and showed beneficial effects on decrease in NT-pro brain natriuretic peptide (BNP) level by 23%, left atrial size by 7%, and symptomatic improvement.[12][13]

In addition, recent studies have reported that sacubitril/valsartan is effective even in patients on dialysis,[14] so that the drug can be widely used in patients with HF in clinical practice. As it is important to evaluate the mortality rate, decrease in hospitalization rate and improvement of symptoms while using the drug, it is also important to monitor whether the drug is working well. In terms of safety, renal function, serum potassium should be monitored, and we should also confirm whether angioedema appears. As for the effect, according to the

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results of the aforementioned studies, we can monitor the effects of the drug by checking improvement in the clinical signs and symptoms of HF. The PARADIGM-HF trial showed an improvement of subjective symptoms using Kansas City Cardiomyopathy Quesionanaire (KCCQ) reported by patients. Another thing to watch out for when monitoring, sacubitril/valsartan specifically inhibits the breakdown of BNP, BNP can be elevated in patients taking this drug without evidence of exacerbations of HF. NT-pro BNP is not a substrate for neprilysin, therefore, NT-pro BNP should be used for patients taking sacubitril/valsartan when a HF aggravation is suspected.

In this respect, this issue of the journal, Kim et al.[15] suggested a good monitoring tool which is objective and also drug-independent. This study aimed to assess that the change in QRS duration is associated with response to ARNIs in patients with HFrEF. According to the study, patients with the QRS shortening of electrocardiogram (ECG) showed favorable recovery of left ventricular systolic function and reverse cardiac remodeling. Therefore, as the use of ARNIs is expanding clinically, it is expected that ECG changes can be used as another useful predictor for monitoring treatment effects.

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