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A NOVEL COMBINATION SACUBITRIL/VALSARTAN IN CHRONIC HEART FAILURE THERAPY

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Advances in the prevention, diagnosis and treatment of cardiovascular diseases in recent years resulted in a significant drop in the deaths from cardiovascular causes. Unfortunately, the same trend was not seen in patients with heart failure (HF). The current treatments for HF with reduced ejection fraction are concentrated on blocking the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). The drugs of choice include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), when ACEIs are not tolerated. Beta-adrenergic blockers and mineralocorticoid receptor antagonists are used as well. However ever under such medical therapy mortality from HF remains around 50%. Therefore, it is essential to come up with more improved versions of treatment.

Sacubitril/valsartan, a supramolecular sodium salt complex of the neprilysin (NEP) inhibitor prodrug sacubitril and the ARB valsartan in a 1:1 molecular ratio, was recently approved in the EU and the USA for the treatment of chronic HF with reduced ejection fraction.

NEP inhibition in HF seems rational basing on its role in metabolism of natriuretic peptides. NEP is an endopeptidase that cleaves atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and CNP. These peptides initiate synthesis of cGMP as secondary messenger resulting in vasodilation, natriuresis, increased renal blood flow and glomerular filtration rate due to RAAS and SNS suppression. In healthy volunteers as well as in patients with HF, NEP inhibitors increase plasma and urinary cGMP levels, and lead to short term hemodynamic improvement, but without significant impact on severe HF.

Attempts to develop NEP inhibitors monotherapy were replaced by combinations with ACEIs but this included the risk of severe angioedema caused by excess bradykinin. The next step was combining an ARB and NEP inhibitor, sacubitril/valsartan.

Sacubitril/valsartan complex forms a stable crystalline structure and is highly water-soluble. The target maintenance dose in HF is one 200 mg tablet, containing 97 mg sacubitril and 103 mg valsartan, twice daily. After administration, sacubitril is rapidly hydrolyzed by carboxylesterase to sacubitrilate, that provides inhibition of NEP; valsartan blocks angiotensin type 1 receptor inhibiting the adverse cardiovascular effects of angiotensin 2 and aldosterone.

The double-blind trial was conducted with random patients of class II, III, or IV HF and an ejection fraction of 40% or less to receive either sacubitril/valsartan (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily). A total of 711 patients (17,0%) receiving sacubitril/valsartan and 835 patients (19,8%) receiving enalapril died; of these patients, 558 (13,3%) and 693 (16,5%), respectively, died from cardiovascular causes. As compared with enalapril, sacubitril/valsartan also reduced the risk of hospitalization by 21%, decreased the symptoms and physical limitations of HF, showed lower proportions of renal impairment, hyperkalemia, and dry cough.

So, understanding the role of the natriuretic peptides and the RAAS provided a new approach in the treatment of HF, and resulted in a highly effective combination of ARB and NEP inhibitor, sacubitril/valsartan.