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Sacubitril/valsartan averts post-myocardial infarction ventricular remodeling and preserves heart function

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Heart failure (HF) is one of the important causes of morbidity and mortality. Though there are several treatments available for HF, it remains a progressive disease that is growing in prevalence. For this, more efficacious therapy is suggested. A recently developed class of drugs called angiotensin receptor neprilysin inhibitors (ARNIs) increases concentrations of natriuretic peptides by inhibiting neprilysin (NEP). NEP inhibition increases angiotensin II (AT II), a potent endogenous vasoconstrictor. It also causes myocardial necrosis and fibrosis. ARNIs, such as sacubitril/valsartan (LCZ696), therefore, combine NEP inhibition with blockade of AT II receptor. Use of this drug has shown improvement of cardiac function, reversal of cardiac remodeling, improvement of exercise capacity, and, most importantly, reduction of cardiovascular mortality and hospitalizations in HF patients [1]. Improvement in exercise tolerance with the use of sacubitril/valsartan in an experimental setting is likely due to noncardiac mechanisms involving neurologic and endocrinologic pathways. Improvement of exercise tolerance with sacubitril monotherapy supports this fact. On the other hand, the monotherapy significantly deteriorated cardiac function and did not reduce myocardial fibrosis due to the unopposed action of AT II. It is found that sacubitril/valsartan therapy increases beta-endorphin (BE) concentrations and improves exercise tolerance. BE elevation might be a potential mechanism of action leading to improvement in exercise tolerance seen with sacubitril/valsartan [1]. HF is common after acute myocardial infarction (MI). MI is one of the major precursors of HF and has been associated with excess mortality. HF during the index MI occurs due to a combination of multiple factors such as myocardial stunning, myocyte necrosis, decompensation of pre-existing HF or acute mitral regurgitation due to papillary muscle dysfunction. Late HF is the consequences of cardiomyocyte death and scar formation occurring alongside ventricular remodeling [2]. PARADIGM-HF (Prospective Comparison of ARNI with ACEI [ACE inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure; NCT01035255) is a randomized, double-blind (DB), parallel-group study that compared synergistic effects of RAAS, and neprilysin inhibition (sacubitril/valsartan) versus RAAS inhibition alone (enalapril). It demonstrated sacubitril/valsartan significantly lowered all-cause and cardiovascular mortality for HF with reduced ejection fraction (HFrEF). This study was one of the largest clinical trials ever conducted in HF (N = 8442) [3]. This trial was terminated early as an overwhelming mortality and morbidity benefit of the ARNI compared to stand-alone RAAS blockade with enalapril was found. The addition of the neprilysin inhibitor component in LCZ696 augments plasma levels of natriuretic peptides such as atrial natriuretic peptide (ANP). ANP has been reported to demonstrate anti-hypertrophic effects in cardiomyocytes and myocardium. Interestingly, when left ventricular function begins to deteriorate, the myocardium expresses natriuretic peptides. It has been demonstrated that increased LV wall stress and LV filling pressures elevate ANP expression in the heart at 1- and 6-weeks post-MI. Studies have shown that gene expression of ANP was significantly reduced with treatment with anti-RAAS drug alone and with the combination of neprilysin inhibitor and ACEI but more with the later. Natriuretic peptides have been shown to inhibit RAAS by reducing renin secretion and angiotensin II production in experimental studies, this may explain the increased attenuation of ANP expression with LCZ696 treatment. Combined ACE and neprilysin inhibition have been shown to reduce LV adverse remodeling post-MI more than ACEI alone [4,5]. Sacubitril/valsartan might reduce the risk of myocardial ischemia. It is possible through hemodynamic mechanisms (e.g., reduction in left ventricular wall stress). This drug combination may also have favorable effects on the coronary circulation by inhibiting the breakdown of C-type natriuretic peptide (CNP) locally and through increases in intracellular cyclic GMP concentration due to the action of circulating natriuretic peptides. CNP, an important substrate for neprilysin, plays an important role in

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the regulation of coronary arterial tone and blood flow. It is cardioprotective in experimental models [6]. There is no doubt that this combination has risen great hope for treatment of heart failure patients particularly post MI HF patients. But as this is a new therapy, there are few barriers to be addressed before initiation. More real-world experiences are needed to gain the confidence of the physicians in general to implement this therapy. More data are required regarding side effects, patient adherence, and long-term effects. A possible long-term effect of sacubitril/valsartan therapy, such as cognitive impairment due to the inhibition of β-amyloid degradation by sacubitril, is a concern for some physicians. PARADIGM-HF study has not shown an increase in cognitive defects with sacubitril/valsartan compared with enalapril. Challenges remain regarding patient selection, initial dose and uptitration of the drug. A low dose of sacubitril/valsartan (24/26 mg twice daily) should be started in patients on low dose enalapril. Subsequently, the dose should be increased every 2–4 weeks, as tolerated, to the target dose of sacubitril/valsartan (97/103 mg twice daily) [3]. Another concern regarding the use of this drug combination is its cost. A study was done to detect whether this therapy is cost-effective or not. The monthly cost for sacubitril/valsartan was found to be $375, and it was $0.96 for enalapril. But the study showed sacubitril/valsartan was cost-effective in comparison to other high-value accepted cardiovascular interventions [7]. In a recent study involving 73 consecutive patients with congestive heart failure and systolic dysfunction who are eligible for the treatment with this combination therapy were enrolled from the Daunia Heart Failure Registry. This study has shown a reduced number of hospitalizations in the treatment group. The cost related to hospitalization is also less in patients treated with ARNI with a p-value < 0.001 [8]. There are several ongoing trials to evaluate the efficacy and superiority in reducing post-MI heart failure. PARADISE-MI study evaluates the efficacy and safety of LCZ696 compared to ramipril, in addition to conventional post-AMI treatment, in reducing the occurrence of the composite endpoint of cardiovascular death, hospitalization due to HF and outpatient HF in post-MI patients [9]. Another study PARALLEL-HF shows the efficacy and safety of LCZ696 in Japanese patients with chronic heart failure and reduced ejection fraction [10]. The results of the studies will be available in 2020. Hopefully, these studies will enlighten us about interesting factors about sacubitril/valsartan therapy and its use in MI patients.

References

[1] M.Y. Maslov, S. Foianini, M.V. Orlov, J.L. Januzzi, M.A. Lovich, A novel paradigm for sacubitril/valsartan: beta-endorphin elevation as a contributor to exercise tolerance improvement in rats with preexisting heart failure induced by pressure overload, J. Card. Fail. 24 (11) (2018 Nov 1) 773–782.

[2] T.J. Cahill, R.K. Kharbanda, Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: mechanisms, incidence and identification of patients at risk, World J. Cardiol. 9 (5) (2017 May 26) 407.

[3] A.J. Sauer, R. Cole, B.C. Jensen, J. Pal, N. Sharma, A. Yehya, J. Vader, Practical guidance on the use of sacubitril/valsartan for heart failure, Heart Fail. Rev. 1-0 (2018 Dec 18).

[4] A.R. Kompa, J. Lu, T.J. Weller, D.J. Kelly, H. Krum, T.G. von Lueder, B.H. Wang, Angiotensin receptor neprilysin inhibition provides superior cardioprotection compared to angiotensin converting enzyme inhibition after experimental myocardial infarction, Int. J. Cardiol. 258 (2018 May 1) 192–198.

[5] T.G. von Lueder, B.H. Wang, A.R. Kompa, L. Huang, R. Webb, P. Jordaan, D. Atar, H. Krum, Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy, Circ. Heart Fail. 8 (1) (2015 Jan) 71–78.

[6] U.M. Mogensen, L. Køber, S.L. Kristensen, P.S. Jhund, J. Gong, M.P. Lefkowitz, A.R. Rizkala, J.L. Rouleau, V.C. Shi, K. Swedberg, M.R. Zile, The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF, Am. Heart J. 188 (2017 Jun 1) 35–41.

[7] T.A. Gaziano, G.C. Fonarow, B. Claggett, W.W. Chan, C. Deschaseaux-Voinet, S.J. Turner, J.L. Rouleau, M.R. Zile, J.J. McMurray, S.D. Solomon, Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction, JAMA Cardiol. 1 (6) (2016 Sep 1) 666–672.

[8] M. Correale, I. Monaco, A. Ferraretti, L. Tricarico, G. Padovano, E.S. Formica, V. Tozzi, D. Grazioli, M. Di Biase, N.D. Brunetti, Hospitalization cost reduction with sacubitril-valsartan implementation in a cohort of patients from the Daunia Heart Failure Registry, IJC Heart Vasc. 22 (2019 Mar 1) 102–104.

[9] Prospective ARNI vs ACE inhibitor trial to determine superiority in reducing heart failure events after MI (PARADISE-MI), [Cited 2019, Feb 02] Available from: https://clinicaltrials.gov/ct2/show/NCT02924727.

[10] Study of efficacy and safety of LCZ696 in Japanese patients with chronic heart failure and reduced ejection fraction. (PARALLEL-HF), [Cited 2019, Feb 02] Available from: https://www.clinicaltrials.gov/ct2/show/NCT02468232.