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REVIEW

Sacubitril/Valsartan and Ivabradine: Two Compounds for Heart Failure with Low Ejection Fraction (EFrEF), Acting by Innovative Mechanisms

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ABSTRACT

The role of two new compounds - Sacubitril/valsartan and Ivabradine in treatment of systolic heart failure (HFrEF) was evaluated. Sacubitril/valsartan (also called as Entresto), together the remaining optimal medical therapy, antagonize HFrEF both strengthening the beneficial effects of natriuretic peptides (NP) and acting against angiotensin II by angiotensin receptor blocker (ARB), valsartan. PARADIGM-HF study has demonstrated that Sacubitril/valsartan is superior to angiotensin-converting-enzyme (ACE) alone in reducing the risks of death and hospitalization for HFrEF. On the contrary Ivabradine, a selective inhibitor of the "funny" channel current present in the sino-atrial node, acts against HFrEF inducing a reduction of heart rate in sinus rhythm patients. This reduction yields an improvement in stroke volume due to the increased of LV diastolic filling, improving the HFrEF symptoms. The results reported in the SHIFT Trial support the importance of heart rate reduction obtained with Ivabradine for improvement of clinical outcomes in HFrEF and confirm the important role of heart rate in the pathophysiology of this disorder. Two drugs act with two diverse and innovative mechanisms and, together the remaining optimal medical therapy, represent an effective improvement in HFrEF therapy.

Key words: Systolic heart failure; Ejection fraction; Sacubitril/valsartan (Entresto); Ivabradine

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INTRODUCTION

Heart failure (HF) is a major public health concern and a more frequent cause of morbidity and mortality in the Western World[1]. In 2012, HF affected more than 5 million Americans. It is responsible for over 1 million hospitalizations and 300.000 deaths/year in USA[2]. Epidemiological studies predict a significant increase in HF in the future, because of an increased life expectancy, despite a dramatic improvement in outcomes of new specific drugs[3]. Hemodynamically, chronic HF can be defined as the inability to provide adequate cardiac output at rest or with exertion[4]. In accordance with Ejection Fraction (EF), HF can be divided in systolic or diastolic HF, with a light prevalence of the last, increasing with advancing age[5]. In detail, HF characterized by low EF% (< 40%) for reduced left ventricular contractile force, is defined as systolic HF (HFrEF). On the contrary in diastolic HF (HFpEF), left ventricular (LV) filling pressure is found to be increased in order to maintain EF% in the normal range[6,7]. HFrEF only can be considered such as a true HF for an irreversible dilation of LV chamber and reduced LV walls'

contractility. In the "steady state", it requires specific treatments for reduced LV contractility and water retention. On the contrary, HFpEF shows normal or lightly increased dimensions of LV chamber and preserved LVEF. It can be considered as an hetereogeneous syndrome mainly present ageing, due to several conditions as lasting systemic hypertension, diabetes, chronic obstructive pulmonary disease, obesity and others. The syndrome requires treatment of the undelying disease and other pharmacological interventions aimed at reducing ventricular-vascular stiffening, pulmonary congestion and accelerated cardiovascular aging.

In the present review, we refer on two drugs recently introduced for treatment of HFrEF.

Systolic HF

The most common cause of systolic HF is related to coronary artery disease (CAD), called as ischemic cardiomyopathy. Primitive and secondary dilated cardiomyopathy can be another cause of systolic HF. Among the secondary types, hypertensive cardiomyopathy is the most frequent form. Valvular heart diseases (mitral valve regurgitation, aortic valve stenosis and/or regurgitation) there are. Viral myocarditis and some arrhythmias are the other, most frequent causes[8]. Extracardiac causes of HFrEF are diabetes mellitus, hyper-or-hypothyroidism, amyloidosis and some drugs. The main HFrEF symptoms include: fatigue and weakness, swelling (legs, abdomen), shortness of brith, chest pain, reduced ability to exercise, etc.

Low cardiac output dependent on systolic HF chiefly induces the activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) in an attempt to increase the peripheral perfusion. Nevertheless, these reactive responses well act in the short term, but have detrimental effects in the long term. A third compensatory mechanism that comes in the second place is the A and B-types natriuretic peptides (NP) effects. They are released primarily in the atrium as consequence of elevated cardiac pressures stretch of atrial myocytes and induce vasodilation and sodium and water excretion[9,10]. The importance of NP is highlighted by the development of the new class of angiotensin-receptor-neprilysin inhibitors (ARNIs).

Therapeutic approaches

Therapy of decompensated HF greatly updated during the past two decades. At inotropic and diuretic agents only[11], Angiotensin Converting Enzyme Inhibitors (ACEIs) were added to act again[12]. Subsequently, Angiotensin Receptor Blockers (ARBs) were developed to antagonize Angiotensin II by competitive antagonism towards its peripheral AT1 receptors with stimulation of AT2 peripheral receptors. Several large trials suggest that the treatment of HF with ARBs is not superior to the treatment with ACEIs, but it is significantly well tolerated[13]. Specifically, cough and angioedema due to degradation of bradykinins and prostaglandins appear lesser frequent with ARBs than ACEIs[14,15]. Recent advances in RAAS blockade have focused the role of Eplerenone in decompensated HF[16]. This drug, in association with optimized baseline therapy, demonstrated significant benefits on the combined end point of cardiovascular death or hospitalization in patients with systolic HF. In 2015, a report on cardiac resynchronization therapy (CRT) in patients with systolic heart failure and QRS interval $\leq$130 ms was published on Europace. In accordance with previous little experiences, CRT evidenced to improve mortality and morbility rates in these patients with left ventricular (LV) mechanical dyssynchrony[17]. An interesting mechanism to antagonize decompensated HF is that of Nesiritide. This is a recombinant human brain natriuretic peptide (BNP) acting such as balanced vasodilator on circulatory system (arteries and veins). Nesidiride acts on arteries to decrease systemic vascular resistance and thereby lowers LV after-load. Its action on veins induces an increase of venous capacitance and thereby lowers left and right heart filling pressures. Thus, the rationale for its use in HF is based on both hemodynamic effects[18]. Tolvaptan is an oral vasopressin V_2 receptor antagonist, able to induce a clearance of free water. The drug induces aquaresis and so, a reduction in body weight, an elevation in sodium level and ameliorate dyspnea. Particularly, removing fluid from the body helps to increase the level of sodium in the blood. Therefore, Tolvaptan can be given in association with reduced doses of loop diuretics in patients with congestive heart failure; it is effective in reversing hyponatriemia and represents a suitable therapeutic option in patients with HF[19,20]. At present, the use of Levosimentan, an agent of the group of calcium sensitizers, must be given intravenously in hospitalized patients only. But, its use is limited for the treatment of acute HF and in a range of other setting characterized by impaired cardiac performance, advanced heart failure, low cardiac output or peri-operative HF[21,22].

Levosimentan has inotropic and vasodilator effects, which impairs myocardial work without a change in myocardial consumption. The compound is produced by the opening of ATP-dependent K^+ channel in the myocytes and smooth vascular muscle cells, causing vasodilation with pre-charge and post-charge reduction and an increase in coronary flow. In addition, it has a positive chronotropic effect caused by the increase of Ca^{++} sensitivity, provoking a rise in myocardial force (inotropic effect). Consequently, the drug induces an improvement in NYHA class of decompensated HF patients. The most common adverse effect of Levosimentan include systemic hypotension, headache, atrial fibrillation, hypokaliemia and tachycardia.

ENTRESTO

Among the drugs recently developed, that can be employed in patients in class II or IV of HF and an ejection fraction of 40% or less, LCZ696 there is. It consists of Angiotensin Receptor Neprilysin Inhibitor (ARNI), sacubitril, and Angiotensin Receptor Blocker (ARB), valsartan in 1:1 molar ratio and was named as Entresto. The compound was evaluated in the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial in patients suffering from HFrEF[23]. The results indicate that Entresto reduced the risk for death from Cardio-Vascular (CV) causes by 20%; reduced the risk of hospitalization for HF by 21%; and reduced HF-related symptoms and physical limitations compared with enalapril, an ACEI (Angiotensin-Converting-Enzyme Inhibitor)[23,24].

Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), that simultaneously suppresses RAAS and enhances Natriuretic Peptides (NP). In particular Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin and adrenomedullin. Consequently its inhibitor, sacubitril, promotes the synthesis of these substances and particularly, of Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) from cardiac myocytes[25]. ANP is synthesized and secreted in atria; BNP is secreted from the ventricles. The ANP and BNP activation induces natriuresis, diuresis, vasodilation, inhibition of the RAAS and the SNS, as well as anti-fibrotic, anti-proliferative and anti-thrombotic effects[26] (Figure 1). These endogenous NP have also an adjunctive, protective mechanism to counteract adverse patho-physiological processes happening

in HF. They stimulate G-protein coupled receptors (GPCRs) on vascular smooth muscle cells which promote the synthesis of the second messenger cyclic guanosine monophosphate (cGMP). In turn, that decreases vascular smooth muscle tone[27]. On the other hand, when vascular smooth tone decreases, peripheral vascular resistance also decreases, and the net effect is decreased capillary hydrostatic pressure and improved cardiac output by decreasing after-load[28].

Another component of Entresto is the ARB, Valsartan. The Val-HeFT Trial (Valsartan Heart Failure Trial) published in 2001, involved a total of 5.000 patients with LV dilatation and reduced LV contractility in II-III-IV NYHA class[29]. The study was performed to evaluate whether valsartan could be further reduce mortality and morbility in these patients respect to ACEI enalapril, considered the cornerstone of the treatment for HFrEF[30,31]. Combined inhibition of the renin-angiotensin system and neprilysin had effect that were superior to those of either approach alone.

The trial PARADIGM-HF was stopped early, after a median follow-up of 27 months and provided evidence that the association of neprilysin with valsartan was more effective than ACE inhibitor enalapril alone in HFrEF treatment. The study indicated the combined end-points: mortality alone and the combined end-point of mortality and morbility (defined as cardiac arrest with resuscitation, hospitalization for HF) were lower with sacubitril/valsartan than with enalapril alone. In addition to these advantages, Entresto was associated with a reduction in cardiovascular death and hospitalization for HF and with slow HF progression. The compound was well tolerated, but showed a higher frequency of symptomatic hypotension in comparison to enalapril and a lower frequency of hyperkaliemia, angioedema, serum creatinine and cough. It must be added that sacubitril/valsartan improved glycemic control compared with enalapril.

It must also be added that the employement of ARB valsartan instead of an ACEI was preferred to avoid angioedema, that frequently occurs as consequence of increased bradykinin levels[32]. In fact, ACEI exposure potentiates bradykinin relaxation in arteries. Possible mechanisms of this potentiation include increased local concentration of bradykinin or direct interaction of the ACEI with B2 receptor (that favors the biological action of kinin). On the contrary, the ARB valsartan did not increases bradykinin. But, Neprilysin inhibition (with sacubitril) also favours bradykinin secretion, that can cause angioedema. Therefore, sacubitril/valsartan is contraindicated in patients with a history of angioedema with an ACE inhibitor or other angiotensin receptor antagonist and in those with hereditary angioedema.

Dosage

Entresto is available as film-coated tablets in several strengths, including 24 mg of sacubitril/26mg of valsartan; 49 mg of sacubitril/51 mg of valsartan; 97 mg of sacubitril/103 mg of valsartan. The recommended starting dose of sacubitril is 49 mg and of valsartan is 51 mg in tablets of Entresto given twice/daily. The dose is doubled after 2 to 4 weeks to the target maintenance of 97 mg of sacubitril/103 mg of valsartan twice/daily. A reduced starting dose of 24 mg of sacubitril and 26 mg of valsartan twice/daily should be used in patients who have not currently taking an ACE inhibitor or an ARBs, or previously taking a low dose of these agents. These reduced doses must be also given to those with severe renal impairment and moderate hepatic impairment[33]. In addition, Sacubitril/valsartan should not be taken concordantly with an ACE inhibitor, and the ACE inhibitor should discontinue 36 hours prior to initiation of Entresto. Main adverse events that could be happen are: hypotension, hyperkaliemia, cough, dizziness, angioedema, renal failure.

Previously, it was affirmed that the starting compensatory mechanism of reduced EF in HF consists in increased resting heart rate (as marker of elevated plasma norepinephrine concentration) in attempt to maintain a normal stroke volume. But, this short-term compensation makes heart failure worse by further enlarging the left ventricle and reducing the pumping ability of the heart. Digoxin was the cornerstone for decades to antagonize systolic left ventricular-impairments[34]. Subsequently, the use of digoxin is constantly declined for the uncertain regarding its clinical efficacy and the risks associated with long-term digoxin use, presumably d dependent on its pro-arrhythmic properties[35-37].

IVABRADINE

Shortly before the introduction in HF therapy of Entresto, a selective inhibitor of the I_f channel current in the pacemaker cells of the sinoatrial node was approved, named Ivabradine[38]. Its mechanism is completely different from that of other drugs used for HF treatment and consists in heart-rate-reduction by inhibiting the cardiac pacemaker current. The reduction happens both at rest and during exercise in decompensate patients in sinus rhythm, mantaining myocardial contractility and atrio-ventricular conduction. The main mechanism consists in the reduction of heart rate that increases the duration of diastole, favoring ventricular filling and, consequently, in improving myocardial perfusion (Figure 2). Ivabradine was approved as a second line drug for symptomatic treatment of patients with chronic heart failure in NYHA class II to IV with systolic dysfunction. The drug must be employed in patients with HF and in sinus rhythm, with a heart rate 75 beats/min or higher, in combination with optimal medical therapy or when beta-blocker therapy is contraindicated or not tolerated.

SHIFT (Services and Housing Interventions for Families in Transition) longitudinal study, published on The Lancet in 2010, was the first study performed with a "funny" current (I_f) inhibitor Ivabradine, in patients with chronic HF, low ejection fraction

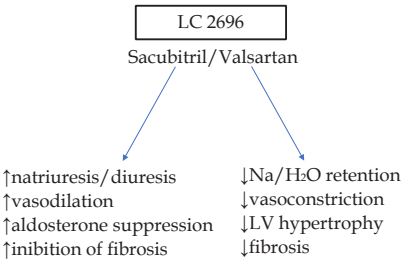

Figure 1 Several both positive and negative effects caused by Sacubitril/Valsartan.

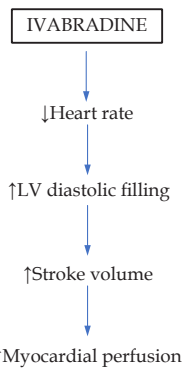

Figure 2 Sequential, hemodynamic effects exerted by Ivabradine in HFrEF.

(</=35%) and sinus rhythm. The study demonstrated that the addition of Ivabradine to the optimal medical therapy including beta-blockers, is associated with a significant reduction of cardiovascular morbility or hospitalization for worsening HF. The benefits were recorded both in ischemic and non-ischemic aetiology of HF[39]. Following the main publication of the trial, a number of sub-studies was conducted in decompensated patients with some important co-mobidities, such as chronic obstructive pulmonary disease, renal dysfunction, diabetes mellitus and low systemic blood pressure. In all these, the efficacy and safety of the drug are similar compared with those observed in patients with HFrEF without these co-morbitities. In the BEAUTIFUL (morBidity-mortality EvAlUaTion of the IF inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) Study, the effects of Ivabradine on patients with coronary artery disease and LV systolic dysfunction were tested. Results reported indicate that Ivabradine, in association with optimal medical therapy, significantly reduces mortality and cardiovascular events in high-risk patients[40].

The reduction of heart rate can be also obtained with other drugs frequently used in HF, such as beta- blockers. But, this reduction happens with a mechanism different from that of Ivabradine. Concerning this, beta-blockers raise negative inotropic and lusitropic effects having unfavorable result on decompensate HF, contrarily to Ivabradine[41,42]. Neverthless, the combination of two drugs (at reduced dosage of beta-blockers) may be employed, obtaining a complementary function in chronic HF. In fact, in CARVIVA-HF (CARVedilol plus IVAbradine) trial, Ivabradine alone or in combination with Carvedilol resulted more effective than Carvedilol alone in improving exercise tolerance and quality of life in HF patients[43,44]. The addition of beta-blockers to Ivabradine induces a lower degree of LV dysfunction progression, the reduction of ventricular arrhythmias and the improvement of quality of life in ICD heart failure patients.

Dosage

The usual recommended dose of Ivabradine is 5 mg twice/daily. After two weeks of treatment, the dose can be increased to 7,5 mg twice/daily if the resting heart rate is persistently above 60 beats/min., or decreased to 2,5 mg twice/daily if the resting heart rate is persistently below 50 beats/min. If the heart rate is between 50 and 60 beats/min., the dose of 5 mg. twice/daily should be maintained. Treatment must be discontinued if heart rate remains below 50 beats/min.

CONCLUSIVE REMARKS

The ACC/AHA recommend the use of Ivabradine and/or sucubitril/valsartan tablets in patients with HF and reduced EF[45]. Two new drugs, added to the optimal medical therapy, act on HF by different mechanisms from other compounds used in systolic HF. Ivabradine acts as inhibitor of the sino-atrial pacemaker, slowing the sinus-beats rate without reducing myocardial contractility. In turn, the heart rate reduction in HFrEF, prolonging the time of LV filling, improves stroke volume and so, myocardial perfusion and the clinical symptoms of decompensated HF. On the contrary, the beneficial effect of Entresto on systolic HF is mainly due to the sacubitril. This inhibits neprilysin, an enzyme that blocks the production of endogenous vasoactive peptides including bradykinin, substance P, and natriuretic peptides. The naprilysin inhibitor, sacubitril increases the production of these substances. In turn, natriuretic and diuretic effects of ANP and BNP are responsible for the improvement of decompensated patients[46]. The second component of Entresto is ARB, valsartan. This is a drug previously employed against HF in the Val-HeFT trial, acting as AT_1 antagonist[29]. On the other hand, AT_1 inhibition stimulates AT_2 receptors that are associated with several beneficial effects, such as local nitric oxide and bradykinin production, vasodilation, anti-fibrotic effects, and anti-proliferative etc.[47]. Thus, the combined angiotensin receptor antagonist and neprilysin inhibitor addresses two of the pathophysiological mechanisms of HF: activation of the RAAS and decreased sensitivity to NP. Furtermore, some aspects of Entresto are still open for future investigations: for example, chronic kidney disease, diabetes mellitus or chronic obstructive pulmonary disease.

Conclusively, Ivabradine and sacubitril/valsartan represent the new-in-class medications for HFrEF, that act with two different mechanisms in comparison to other compounds. Ivabradine can be used in HF patients with sinus rhythm only and utilizes the reduction of heart rate to obtain an increase in stroke volume as a consequence of LV filling prolongation. On the contrary, the innovative mechanisms of sacubitril/valsartan is due to the strengthening of NP consequent to neprilysin inhibition. In Entresto, the ARB valsartan performs its beneficial effects by inhibiting AT1 receptors and stimulating AT2 receptors[48].

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