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The introduction of sacubitril + valsartan as therapy in heart failure. Which patients can benefit the most from this novel drug?

Rahil S. Hussain, Manpreet S. Kumar, Kelly Saka-Patrick, Ali J. Rezaee

Department of Hypertension, Internal Diseases and Angiology, Medical University of Warsaw

INTRODUCTION

The 5-year mortality rate for congestive heart failure (CHF) is similar to that of many cancers, and the condition is responsible for high rates of hospitalisation and intensive outpatient care [1]. CHF affects around 1–2% of the adult population in developed countries, thus is it can be assumed around 600,000 to 700,000 patients in Poland may be affected [2, 3]. 5% of all medical and geriatric admissions are due to CHF and it is the number one cause of hospitalization in patients' aged 65 and over, amassing approximately 2% of the entire health care budget within European countries [2].

KEY SYSTEMS INVOLVED IN CHF

Remodelling of the renin–angiotensin–aldosterone system (RAAS) plays a crucial role in the pathophysiology of CHF. Numerous randomised controlled studies have shown that preventing remodelling improves mortality and morbidity in CHF patients [5, 6]. Renin is released from the juxtaglomerular cells in the kidney as an attempt to restore perfusion pressure within the organ. Renin has enzymatic activity and converts angiotensinogen to angiotensin I, which is then converted into angiotensin II by angiotensin converting enzyme (ACE) in the lungs. Angiotensin II has a number of systemic effects however 2 play a pivotal role in inducing hemodynamic changes; systemic vasoconstriction and induction of the release of aldosterone [7, 8]. Aldosterone regulates blood pressure by influencing increased sodium and water reabsorption in the kidneys, but also promotes endothelial dysfunction and cardiac fibrosis [8]. Furthermore angiotensin II also has an affect on the cardiomyocytes, causing apoptosis and hypertrophy of these cells, eventually leading to the development of myocardial fibrosis [8]. These effects coupled together are the main constituents of cardiac remodelling, which is a maladaptive response causing cardiac dysfunction and ventricular dilation [8].

When up-regulation of the RAAS occurs, the body uses the natriuretic peptide system in an attempt to counter-act the detrimental effects. Vasoconstriction and the sodium and water retention caused by activation of RAAS causes an increase in ventricular preload and afterload. This leads to an elevation in wall stress causing the release of pre-pro B-type natriuretic peptide (BNP), which is then cleaved to BNP and N-terminal proBNP (NT-proBNP) [5]. BNP will then cause a decrease in central venous pressure and systemic vascular resistance along with an increase natriuresis, thus counteracting the activation of RAAS. BNP isn't the only natriuretic peptide involved in the haemostatic control; in fact upon atrial stretch the atria produces pre-proatrial A-type natriuretic peptide, which is then converted into atrial natriuretic peptide (ANP) by the cardiac transmembrane serine protease corin [5, 9]. ANP has similar physiological effect as

BNP in causing a decrease in preload and afterload via reduction of cardiac output and systemic blood pressure [5]. Strategies have been developed for modulation of this pathway in patients with CHF. The first strategy involved giving individuals' nesiritide, a recombinant human BNP. Initial results were promising and showed a positive therapeutic effect on natriuresis and haemodynamics in CHF patients. However, in a large randomised controlled trial, nesiritide failed to show therapeutic benefits for CHF patients [10]. A recombinant ANP (carperitide) is currently being used in Japan for acute HF treatment, though there is no robust evidence for supporting this practice [5, 11]. The second strategy was to inhibit degradation of vasoactive peptides, by inhibiting neprilysin thus allowing enhanced activity of endogenous natriuretic peptides [5]. Neprilysin is a zinc-dependent metalloprotease, which is found abundant in a number of tissues but has the highest concentrations within in the kidney.

NEPRILYSIN INHIBITION

Monotherapy

Initially inhibition of neprilysin was successful using a formulation of oral raceodotril and intravenous candoxatrilat, results showed increased urinary excretion of ANP and natriuresis [5]. However a study on chronic use of candoxatril showed that the initially reduction in blood pressure was not sustained long term and thus further development was stopped [12]. The reason behind the failure of long-term blood pressure control might be due to neprilysins ability to breakdown angiotensin II [5]. Therefore independent inhibition of neprilysin would amplify the systemic effects of angiotensin II to the point where it is able to override the counter affects of ANP and BNP.

Dual therapy with ACE inhibition

Due to drawback of monotherapy the next step taken was to combine an ACE inhibitor with a neprilysin inhibitor. Consequently the drug omapatrilat (a combined ACE inhibitor and neprilysin inhibitor) was used in a large randomised controlled trial against enalapril (ACE inhibitor) in which 5570 patients with severe HF participated [13]. The results *of Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events* (OVERTURE) trial showed that omapatrilat was not superior to the ACE inhibitor, as deaths from any cause or heart failure hospitalisations were not reduced by omapatrilat [5, 13]. The group receiving omapatrilat also showed higher rates of angioedema, which can be explained due to both neprilysin and ACE inhibition, along with omapatrilat induced inhibition of aminopeptidase P (which normally would catabolise bradykinin) [5]. Both of these enzymes break down omapatrilat and bradykinin. Therefore, inhibition leads to an unintended excessive potentiation of bradykinin and high rates of angioedema. This ultimately lead to the discontinuation of further clinical development of omapatrilat [5, 13].

Dual therapy with angiotensin receptor blocker

The next logical step was to combine a neprilysin inhibitor with an angiotensin receptor blocker (ARB) as a solution to overcome the issue encountered with omapatrilat. This lead to the production of the first angiotensin receptor-neprilysin inhibitor (ARN-I) drug, with the aim of inhibiting neprilysin while blocking the adverse effects of potentiation of RAAS and the risk of angioedema [14–16]. ARN-I was formerly known as LCZ696, and is made up of a neprilysin inhibitor prodrug sacubitril and the ARB valsartan [19]. There was a prospective comparison of ARN-I with ACE-I to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF), which concluded that ARN-I was superior to enalapril in reducing the risks of death and hospitalization for heart failure. Allowing the drug to be marketed in the EU and USA [3, 5].

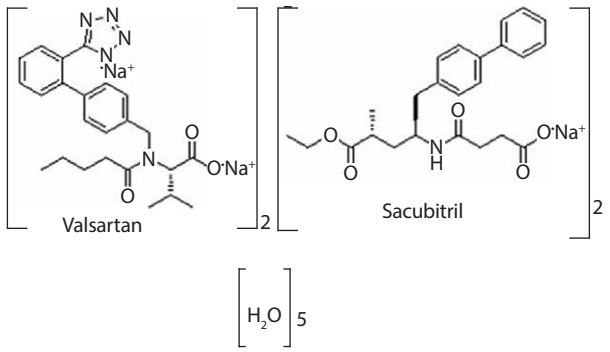
PHARMACODYNAMICS OF ARN-I

ARN-I is formed in a 1 : 1 molecular ratio (fig. 1) of sacubitril and valsartan [3]. The drug has a stable, highly water soluble crystalline structure, containing 6 valsartan and 6 sacubitril anionic molecules complexed with water and sodium cations [3]. Upon oral intake, the complex fully dissociates into sacubitril and valsartan. Sacubitril is rapidly metabolised to its active neprilysin inhibitor LBQ657 by enzymatic cleavage of its ethyl ester [17]. Valsartan inhibits RAAS by acting as a selective type 1 (AT_1) angiotensin receptor antagonist and in so preventing the binding of angiotensin II [3].

PHARMACOKINETICS OF ARN-I

After oral administration of a single dose of ARN-I (200–1200 mg) in healthy adult volunteers maximum plasma concentration (C_{max}) of sacubitril and valsartan at times

Figure 1. Chemical structure of LCZ696 (modified from [19]).



(t_{max}) of 0.5–1.1 and 1.7–2.2 respectively [3]. With the t_{max} for LBQ657 being 1.9–3.5 h [3, 15]. Oral bioavailability of sacubitril is estimated to be equal to or more than 60% and the bioavailability of valsartan is increased in comparison to a single agent valsartan drug formulation, such that a 103 mg dose of ARN-I was bioequivalent to a single agent valsartan 160 mg dosage [3, 15]. ARN-I can be administered with or without food.

A steady state C_{max} was obtained for valsartan, sacubitril and LBQ657 after 3 days of twice daily administration [3, 18]. All 3 are highly bound to plasma proteins (94–97%) and have wide spread distribution across the body, with the average volumes of distribution for valsartan and sacubitril being 75 L and 103 L, respectively [18]. LBQ657 is not further metabolised, however valsartan is partially metabolised to the hydroxyl metabolite valeryl-4-hydroxy valsartan by cytochrome P450 2C9 [3]. Main excretion of sacubitril and LBQ657 is through urine (52–68%), whilst valsartan is predominantly excreted via the faces (86%) [3, 18]. The mean half lives of valsartan, sacubitril and LBQ657 are ≈ 9.9, ≈ 1.4, and ≈ 11.5 h, respectively [18]. The pharmacokinetics of ARN-I were not affected by the patients' sex, however exposure to valsartan and LBQ657 was increased in elderly patients with an age of 65 and above, but not sufficient enough to require dosage adjustment [3].

Due to minimal involvement of CYP enzymatic activity in the metabolism of ARN-I, the drug is not expected to interact with other drugs that induce or inhibit the CYP isoenzymes [18]. However concomitant use with lithium may cause a spike in lithium serum concentrations and result in lithium toxicity [3, 18].

We know ACE inhibitors, ARB, mineralocorticoid/aldosterone receptor antagonists and β-blockers have been the cornerstone of therapy for CHF patients with reduced ejection fraction, because of their proven efficacy and benefits on mortality and morbidity in large clinical trials [3, 4]. It is apparent that ARN-I's possibly have a role to play in patients with CHF. Due to the results of the clinical trials on sacubitril + valsartan, the FDA in the USA approved *Entresto* (sacubitril + valsartan) on a fast track basis in July 2015 (US Food and Drug Administration, 2015). The indicated use is to lower the risk of CV death and hospitalization due to HF in those with NYHA II–IV. The clinical uses and trials of sacubitril + valsartan are described below.

CLINICAL USES OF SACUBITRIL + VALSARTAN

Evidence shows that sacubitril + valsartan can only be administered to patients with heart failure and a reduced ejection fraction (HFrEF), however ongoing trials may posit a role for the drug in heart failure and a preserved ejection fraction (HFpEF) and in hypertension [27, 31, 48–50]. The aims of treatment using sacubitril + valsartan in chronic heart failure involve reducing mortality and hospitalisation [30].

In regards to sacubitril + valsartan's clinical indications, a patient's ejection fraction, New York Heart Association (NYHA) classification in regards to symptomatology and concentration of N-terminal pro B-type natriutetic peptide (NT-proBNP) or B type NP peptide (BNP) were used to deduce clinical efficacy in heart failure [20].

Pathophysiological changes in heart failure patients

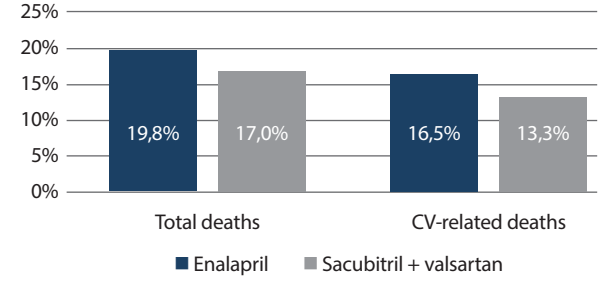
Heart failure presents typically with symptoms such as dyspnoea that may be at rest or at varying degrees of exertion, ankle swelling, fatigue/weakness, arrhythmia, a persistent cough and angina [22]. The severity of heart failure symptoms are classified according to the NYHA functional classification system [40]. Some signs associated with heart failure include, crepitations evident from lung auscultation, peripheral oedema and an increased jugular venous pressure [40].

Mechanistically, in heart failure, there is a reduced cardiac output which is insufficient in meeting systemic oxygen and nutrient demands [40]. Heart failure may also occur with increased intra-cardiac pressures, which occur to maintain cardiac output at the expense of the raised pressure [40].

Heart failure with reduced ejection fraction

Based on the PARADIGM-HF study, sacubitril + valsartan is more likely to be second line drug in patients with symptom persistence after ACE inhibitor use when treating patients with chronic heart failure with a reduced ejection fraction [27]. The study defined heart failure with a reduced ejection fraction (HFrEF) (or systolic heart failure) as an ejection fraction ≤ 40%, this was later amended in the study and defined as ≤ 35% [26, 27]. Ejection fraction can be defined as the amount of blood pumped out of the ventricle with each contraction [21]. The European Society of Cardiology (ESC) guidelines regarding chronic heart failure based on the PARADIGM-HF study, indicate the type of patient suitable for sacubitril + valsartan treatment [27]. The PARADIGM-HF study consisted of participants that presented with a NYHA classification of II, III or IV (symptomatic patients), and an NT-proBNP value or BNP value of ≥ 600 pg/ml or ≥ 100 pg/ml, respectively [26]. Also included in the study were participants that had been hospitalised within the past 12 months that had a BNP level of 100 pg/ml or an NT-proBNP of ≥ 400 pg/ml [26]. It can be discerned from this trial that in both chronic HFrEF participants that had not been hospitalised in the past year and participants that had, sacubitril + valsartan was more effective than the ACE-I enalapril in reducing mortality and was therefore more beneficial therapeutically [26]. Specifically, when compared to enalapril, only 13.3% of the sacubitril + valsartan group died of cardiovascular associated causes, meanwhile the figure for the enalapril group was 16.5% [26]. Moreover, whilst 17% of the sacubitril + valsartan group died due to all causes, the mortality for the enalapril group was 19% (fig. 2) [26]. The superiority of sacubitril + valsartan over enalapril in HFrEF treatment was further proven due to a reduction of all cause mortality by 16% and cardiovascular mortality by 20% [26]. Compared to enalapril, sacubitril + valsartan was also more effective in preventing heart failure progression, evidenced by 21 participants needing treatment to prevent death or one primary event within the trial period, whilst 32 participants administered valsartan required further treatment [26]. It can be deduced from this evidence that to reduce symptom progression, hospitalisation or mortality, the administration of sacubitril + valsartan alongside β-blockers and mineralcorticoid receptor antagonists is a viable treatment option after failed ACE-I or ARB treatment [27]. Mechanistically, the therapeutic superiority of sacubitril + valsartan in reducing cardiovascular changes in HF is due to it combining both RAAS inhibition via valsartan and increased ANP and BNP production via sacubitril inhibition of neprilysin (NEP) [32]. In heart failure, natriuretic peptides are produced due to left ventricle pressure increases and fluid overload [29]. The sacubitril component of sacubitril + valsartan inhibits NEP, preventing ANP and BNP degradation and augmenting their homeostatic release [33]. This results in cyclic guanosine-3,5-monophosphate (cGMP) synthesis, which mediates the functions of ANP and BNP [29]. With sacubitril mediated increases in ANP, renin production is inhibited, glomerular filtration rate is increased, sodium and water retention are reduced and cardiomyocyte and therefore heart size changes are minimised [33, 40]. These physiological changes reverse the changes that occur in heart failure [32]. Increased BNP also reverses the effects of HF, specifically through BNP regulation of fibroblast proliferation, which reduces cardiac fibrosis [32]. The effects induced by sacubitril on ANP and BNP do not occur when ACE-Is or ARBs are used, rather they mediate RAAS inhibition without ANP or BNP increases, reducing their overall efficacy in HF treatment [23].

Figure 2. The effect of sacubitril + valsartan on total death ($p \leq 0.001$) and cardiovascular-related mortality ($p \leq 0.001$) [26].



CV – cardiovascular.

The model patient for sacubitril + valsartan use can be deduced from the PARADIGM-HF study. Namely, the patients that were eligible for administration of the drug and those in which the drug was most effective [28]. Sacubitril + valsartan is effective in individuals above 18 and in all age groups was more effective than enalapril [26]. The mean age of participants was 64, however as highlighted by NICE, it must be stated that heart failure patients are more likely to be older (between 76 and 80, for men and women respectively) [27]. Another advantage relative to ARB monotherapy is that sacubitril + valsartan's pharmacokinetics remained the same regardless of age, in com-

parison valsartan's half life for example, was increased by 30% in older patients [19]. In the PARADIGM-HF study both men and women with HFrEF responded equally to treatment [24, 26]. Specific to the patient demographics in Poland, the study highlighted that sacubitril + valsartan administration resulted in lesser mortality than enalapril in central European participants [26].

In regards to symptoms, sacubitril + valsartan is mainly indicated for patients designated to NYHA class II or III and can be indicted in patients with a slightly elevated systolic blood pressure (the mean being 122 mmHg in participants) [26].

Heart failure with preserved ejection fraction

As evidenced by the PARAMOUNT phase II trial, sacubitril + valsartan may potentially be indicated as a replacement for ARBs in individuals with chronic heart failure and a preserved ejection fraction (HFpEF) [22]. It has been posited that the functional and structural changes to the myocardium in HFpEF may occur due to mechanisms triggered by co-morbidities [39]. ARBs may be potentially effective in HFpEF treatment due to some reversal of the pathological mechanisms in HFpEF, namely the reduction of cGMP availability [39]. Sacubitril + valsartan may also be beneficial in HFpEF due to its blood pressure lowering effects, which may aid in normalising the hemodynamic abnormalities in HFpEF [38].

In the PARAMOUNT trial, as in the PARADIGM-HF study, male and female participants included were symptomatic and predominately in NYHA class II and III with an NT-proBNP of at least 400 pg/ml, they were also already being administered diuretics and had a systolic blood pressure below 140 mmHg [31]. A decrease in NT-proBNP after 12 weeks was the primary endpoint in this study and therefore the barometer of efficacy of sacubitril + valsartan in HFpEF treatment [31]. After 12 weeks, participants administered the drug had a greater decrease in NT-proBNP which occurred earlier in the trial, compared to participants administered valsartan alone [31]. In regards to mortality and the development of serious adverse effects sacubitril + valsartan also fared better, with 15% of participants being affected by serious adverse effects or death whilst the figure was 20% in those that had been administered valsartan [31]. These results highlight that sacubitril + valsartan is more effective than valsartan in preventing mortality and morbidity in those with chronic HFpEF. By week 36 of the study, in participants administered sacubitril + valsartan there was also a reduction in the chronic HFpEF induced remodelling of the left atrium. Specifically, left atrial volume (LA vol) decreased from 67 ml to 65.3 ml after 36 weeks of sacubitril + valsartan use whilst valsartan use alone did not affect left atrial remodelling, evident by LA vol essentially being unchanged in these participants [31].

Hypertension

Due to the blood pressure lowering effects of both sacubitril and valsartan as monotherapuetic agents, sacubitril + valsartan may have some indication in hypertensive patients [34]. The PARADIGM-HF study, PARAMOUNT trial and PARAMETER study highlight the effectiveness of sacubitril + valsartan in reducing blood pressure [26, 43]. Specifically, in the PARADIGM-HF study, sacubitril + valsartan reduced mean systolic blood pressure by 3.2 ± 0.4 mmHg after 8 months, in normotensive patients (with a blood pressure of 122/150 mmHg at baseline) [26]. Likewise, the PARAMOUNT study corroborates with this study in highlighting the effectiveness of the drug in blood pressure reduction. In particular, after 12 weeks of sacubitril + valsartan use, those with a controlled mean sitting blood pressure of 136/79 mmHg experienced a reduction of 9.3/4.9 mmHg in their blood pressure, whereas valsartan only reduced blood pressure values by 2.9/2.1 mmHg [31]. Similarly, at 36 weeks, sacubitril + valsartan was more effective relative to valsartan monotherapy in reducing both diastolic and systolic blood pressure. The drug reduced blood pressure values by 7.5/5.1 mmHg, whereas valsartan reduced values only by 1.5/0.34 mmHg [31]. These findings highlight the possibility of sacubitril + valsartan being used to treat uncontrolled/controlled hypertension [31, 34]. Lastly, the PARAMETER study also revealed potential for sacubitril + valsartan to be used as an anti-hypertensive agent. The study involved the use of sacubitril + valsartan by participants ≥ 60 years of age, that had an increased pulse pressure and mild to moderate systolic blood pressure [43]. The hypertensive changes in these participants occurred secondary to stiffening and aging of the aorta and other large arteries [43]. The study found that in both short term (12 weeks) and long term (52 weeks) of sacubitril + valsartan use, central aortic systolic blood pressure values were reduced by 3.7 mmHg greater than olmersartan [42]. At 52 weeks, participants administered sacubitril + valsartan required

less additional anti-hypertensive agents, relative to those administered olmersartan [42]. This study reveals the potential use of sacubitril + valsartan in elderly patients with hypertension.

ADVERSE EFFECTS & CONTRAINDICATIONS OF SACUBITRIL + VALSARTAN

The main adverse effects associated with sacubitril + valsartan use include hypotension, hyperkalaemia, cough, dizziness and renal failure, meaning caution should be applied when administering the drug in patients with any of these pre-existing comorbidities [19]. These adverse effects were substantial enough to warrant participant withdrawal during the PARADIGM-HF study [26]. Due to its effect on potassium concentration, sacubitril + valsartan is contraindicated in patients with a serum potassium concentration of more than 5.4 mmol/L [20]. Similarly, due to it reducing in blood pressure and potentially inducing symptomatic hypotension, sacubitril + valsartan is contraindicated in patients with a blood pressure below 100 mmHg [20].

New onset atrial fibrillation occurred more so in sacubitril + valsartan use than in enalapril use (84 and 83 patients, respectively, developed fibrillation after sacubitril + valsartan and enalapril use) [26].

In both HFrEF and HFpEF the inhibition of RAAS during treatment can cause angioedema to occur, which is a potentially fatal adverse effect [25]. In the PARADIGM-HF study, 19 cases of angioedema occurred after sacubitril + valsartan use whereas only 10 cases of angioedema occurred in participants administered enalapril [26]. Due to the increased risk of angioedema in African Americans, dosage adjustments may be needed when administering the drug [30]. In patients with a history of angioedema following ACE-I use, sacubitril + valsartan may also require temporary cessation of administration or may be contraindicated [22].

Sacubitril + valsartan caused symptomatic hypotension in more participants, with 14% developing symptomatic hypotension and 2.7% developing hypotension below 90 mmHg, after use [26]. One the other hand, only 9.2% participants developed symptomatic hypotension after enalapril use, with 1.2% of participants experiencing a drop in systolic blood pressure below 90 mmHg [26]. Although the administration of sacubitril + valsartan did not have to be stopped due to hypotension, it is clear that it has an increased risk over enalapril in causing symptomatic hypotension.

Another adverse effect of sacubitril + valsartan use may be the exacerbation of renal dysfunction in patients with pre-existing renal disease, for example renal artery stenosis, in severe congestive heart failure or in chronic kidney disease [19]. However, the risk of development of renal adverse effects is lower in sacubitril + valsartan use than in enalapril use [26]. This is evidenced by only 8 participants that were administered the drug going on to develop end stage renal failure, which was less than those administered enalapril [26].

In pregnant women the inhibition of RAAS when treating systolic or diastolic HF with sacubitril + valsartan also leads to foetal toxicity, contraindicating the drug's use during pregnancy [22]. Use of sacubitril + valsartan in the second and third trimester is especially associated with foetal death [19]. Sacubitril + valsartan is also contraindicated in during lactation [19].

It has been hypothesised that long-term sacubitril + valsartan may be associated with Alzheimer's disease, secondary to the increased deposition of amyloid-β-plaques (Aβ) [36]. Mechanistically, NEP causes the degradation of Aβ, however when NEP is inhibited by sacubitril + valsartan, Aβ may accumulate [36]. While studies into the effect of sacubitril + valsartan on mental functioning revealed no detriment to memory or cognition, it remains to be seen if long term the drug may contribute to the disease's pathogenesis [36]. Evidence of NEP inhibition and Aβ accumulation, is revealed by the accumulation of Aβ in the brain of healthy human subjects after sacubitril + valsartan use [41]. Similarly, in animal models involving NEP inhibition by thiorphan, there was increased deposition of Aβ in the hippocampus of mice [37].

DOSAGE OF SACUBITRIL + VALSARTAN

In regards to dosing, it is recommended that 49 mg sacubitril + 51 mg valsartan is administered orally twice a day (b.i.d) [22, 27]. Following 2 to 4 weeks, the dosage is doubled to 97 mg sacubitril + 103 mg valsartan, which is the target dose for the drug [27]. The patient's tolerance to

the drug, based on the development of adverse effects, must be taken into consideration when increasing the dosage of the drug. The TITRATION study, involving patients with HFrEF (≤ 35%) compared sacubitril + valsartan use to ACE-I/ARB use to identify any adverse effects associated with increasing the dosage of sacubitril + valsartan from 50 mg b.i.d to 200 mg b.i.d (the target dose) over 3 weeks and/or 6 weeks [44]. From the study, it was identified that up titrations of sacubitril + valsartan were both safe and tolerable [45].

In the treatment of systolic hypertension, sacubitril + valsartan was clinically effective at dosages of 100 mg, 200 mg or 400 mg, administered once daily [42].

Identifying target patients

Understandably, due to the results in the major trials outlined above, there has been considerable debate as to whether there should be a realignment of HF treatment with ARN-I's at the forefront of therapy. The consensus seems to be that ARN-I use can be beneficial in specific situations, but which group of patients will benefit the most from this? Which groups may be at risk of adverse effects if prescribed medications such as *Entresto*?

An important factor to be considered is that the PARADIGM-HF trial was somewhat selective in the patients included. During the run-in period of acclimatisation of patients to sacubitril + valsartan 12% of them were withdrawn due to severity of side effects including cough and renal dysfunction. Thus, in evaluating the use of *Entresto* in the clinical setting this factor should be taken into account, as many may not tolerate the side effects. Angioedema, therefore may become a concern. Another area of worry is the affect on Amyloid-β (Aβ) metabolism in the brain. Neprilysin deficient knockout mice have shown to have an increased level of Aβ deposition and behavioural impairment reminiscent of Alzheimer's [46]. Neprilysin is thought to be involved in the degradation of Aβ [47]. Thus its inhibition may lead to an increased rate in Aβ deposition and perhaps increase the risk of development of dementia. Whilst these possible adverse affects were not measured in the PARADIGM-HF trial, a small study on 35 healthy volunteers showed little change in the overall levels of Aβ after administration of LCZ696 (sacubitril) [49]. It should be noted however, that this study lasted merely 2 weeks, and thus may not be a reliable indicator of whether or not LCZ696 may be partially causative in the development of a disease that usually takes 10 or even 20 years to develop. Due to this, it may be wise to be more cautious with long-term prescribing of *Entresto* in those patients with mild HF that are to be medicated for 10–20 years.

CONCLUSIONS

The limitations in PARADIGM-HF outlined above and other questions surrounding sacubitril + valsartan use, are in the process of being answered. Current trials are in progress to further elucidate newer groups of HF patients that may benefit from use of ARN-I's. The HFN--LIFE trial is investigating use of sacubitril + valsartan in those with advanced heart failure due to LV dysfunction, by analysing changes in NT-proBNP levels [48]. PARADISE-MI aims to assess use of ARN-I's versus ACE-I in preventing post MI heart failure events [49]. Finally, PARAGON-HF is a key ongoing trial comparing the use of sacubitril with valsartan and the effects on morbidity and mortality in those with HFpEF. Importantly, cognitive function will be included as an outcome measure [50]. The completion of these trials will provide valuable data to further evaluate subsets of patients that will benefit from use of ARN-I's such as *Entresto*. The conclusions gained from these trials will identify whether the results seen in those with HFrEF are also consistent with a wider array of patients with HF.

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CORRESPONDENCE:

Kelly Saka-Patrick
Department of Hypertension, Internal Diseases and Angiology,
Medical University of Warsaw,
02-091 Warsaw, ul. Żwirki i Wigury 81

STRESZCZENIE

Niewydolność serca stanowi w krajach rozwiniętych istotną przyczynę zwiększonej chorobowości i śmiertelności. Przewlekła aktywacja układu RAAS (*renin–angiotensin–aldosterone system*) jest związana z przebudową serca i pogorszeniem jego funkcji. Wcześniejsze interwencje farmakologiczne polegały na zahamowaniu układu RAAS poprzez zastosowanie β-adrenolityków, inhibitorów konwertazy oraz antagonistów receptora dla aldosteronu. W ciągu ostatnich dekad dowiedziono protekcyjnego działania przedsionkowego peptydu natriuretycznego (ANP, *atrial natriuretic peptide*) i mózgowego peptydu natriuretycznego (BNP, *brain natriuretic peptide*) w niewydolności serca i rozpoczęto badania mające wyłonić leki hamujące uszkodzenie serca u chorych z jego niewydolnością. Początkowo stosowano rekombinowane peptydy natriuretyczne, jednak wyniki badań były niekorzystne. Kolejne badania dotyczyły neprylizyny, enzymu degradującego peptydy natriuretyczne. Wcześniej prowadzone badania nie wykazały przewagi leków hamujących neprylizynę względem inhibitorów konwertazy oraz sartanów. Przełom nastąpił po badaniu PARADIGM-HF. Wykazano w nim , że u chorych ze skurczową niewydolnością serca połączenie antagonisty receptora dla angiotensyny i inhibitora neprylizyny zmniejsza istotnie bardziej niż enalapryl śmiertelność całkowitą, sercowo-naczyniową i liczbę hospitalizacji. Chociaż wymienione połączenie zostało zarejestrowane przez FDA (*US Food and Drug Administration*), to użycie leku jest ograniczone z powodu małego doświadczenia z jego stosowaniem oraz działań ubocznych, m.in. obrzęku naczynioruchowego. Lek jest zalecany w niewydolności skurczowej serca zamiast inhibitorów konwertazy u chorych objawowych mimo optymalnego leczenia. Niezależnie od wyników badania PARADIGM-HF nadal pozostaje wiele pytań o skuteczność połączenia i jego bezpieczeństwo w różnych populacjach chorych z niewydolnością serca.

Słowa kluczowe: niewydolność serca, PARADIGM-HF, sakubitryl, walsartan

ABSTRACT

Heart failure (HF) is a significant cause of morbidity and mortality in developed countries. Chronic activation of RAAS has been implicated in remodeling of the heart and progression of HF. In the past pharmacological therapies have been aimed at suppression of RAAS with β-blockers, ACE inhibitors, and mineralocorticoid receptor blockers being the cornerstone of HF therapy. Over the recent decades as the protective role of natriuretic peptides (ANP and BNP) became more clear in HF, efforts have been made in manipulating these vasoactive peptides to counter remodeling of the heart in HF patients. Initial strategies involved use of recombinant natriuretic peptides, however trials failed to show therapeutic benefits in HF patients. The next strategy was inhibition of neprilysin, an enzyme that degrades natriuretic peptides, with the goal of increasing endogenous levels of ANP and BNP. Over the years multiple trials failed to demonstrate superiority of various combination of drugs targeting neprilysin inhibition over the standard therapy (ACE inhibitor or ARB). A breakthrough was finally made when PARADIGM-HF trial showed that combination therapy with angiotensin receptor-neprilysin inhibitor (ARN-I) significantly lowered cardiovascular mortality and hospitalization as well as all-cause mortality in HFrEF (heart failure with reduced ejection fraction) patients compared to treatment with a proven dose of ACE inhibitor (enalapril 10 mg). Although ARN-I is FDA (US Food and Drug Administration) approved, currently its use remains limited in many countries because of lack of clinical experience and its potential life-threatening adverse effects (e.g. angioedema). It is recommended as a second-line agent in place of ACE inhibitor in HErEF patients who remain symptomatic despite optimal treatment with HF drugs. Despite the valuable lessons learned from PARADIGM-HF trial many questions are still left unanswered in regard to efficacy and safety of ARN-I in other subset of patients with HF who may benefit from its use.

Key words: heart failure, PARADIGM-HF, sacubitril, valsartan

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