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ORIGINAL PAPER

ARNIs: balancing "the good and the bad" of neuroendocrine response to HF

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Abstract

Background A new class of drugs—angiotensin receptor, neprylisin inhibitors, ARNI—has shown to be prognostic superior in HFrEF to the sole inhibition of the renin–angiotensin axes with enalapril. The ultimate mechanism of action of ARNIs is unknown.

Aim We have considered that ARNI exerts a positive modulation of the neuroendocrine balance, with enhancement of the physiological diuresis and dilatation due to neprylisin inhibition by sacubitril. This represents a shift in HF medical therapy always directed to counteract (with inhibitors of the renin–angiotensin system, beta blockers or inhibitors of aldosterone) the so-called "bad" neuroendocrine response. Development of ARNI, on the contrary, has led to consider the neuroendocrine response to HFrEF from a different angle, which is to say that the activation is not always deleterious, but it could also be beneficial. This concept is highlighted by the enhancement of the activity of atrial natriuretic peptide, induced by sacubitril/valsartan in the PARADIGM trial, and found as proof from early studies on untreated patients with constrictive pericarditis. The possibility that sacubitril inhibition of neprylisin acts by enhancing substance P and gene-related calcitonin peptide is also considered, as well as the negative effect of neprylisin inhibition.

Conclusions The beneficial effects of ARNI are related, in part at least, to a positive modulation of the neuroendocrine response to the disease, resulting in an increase of physiological diuresis and dilatation.

Keywords ARNI · HF · Sacubitril · Valsartan

Introduction

Irrespective of the causes or the clinical manifestations of chronic heart failure with reduced ejection fraction (HF_rEF), or even the criteria used to define it, it is irrefutable that therapy with renin–angiotensin antagonists, beta-blockers, and aldosterone inhibitors is beneficial [1–4]. This and other findings led to the general belief that prolonged neuroendocrine activation in HF_rEF is deleterious and that it is therapeutically important to reduce it [5].

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The new pharmacological class of angiotensin receptor-neprylisin inhibitors (ARNIs) in the PARADIGM-HF study and others challenged this belief by showing that pharmacological enhancement of "some" neuroendocrine response, i.e., endogenous natriuretic peptides, is actually beneficial [6, 7].

A series of PARADIGM-HF post-hoc analyses and further studies with sacubitril/valsartan [6–11], a first-in-class of ARNIs, consolidated the superiority of this new HFrEF therapeutic strategy, denominated Neurohormonal Modulation [11], over the classical Neurohormonal Blockade.

We believe that the understanding of this conceptual shift in the treatment of HF_rEF deserves further considerations. Therefore, a group of cardiologists from Italy and Portugal interested in CHF met at the University of Ferrara to discuss the underlying mechanisms of the success of ARNIs.

We have considered that ARNI exerts a positive modulation of the neuroendocrine balance with enhancement of the physiological diuresis and dilatation due to neprylisin inhibition by sacubitril. This represents a shift in HF medical therapy always directed to counteract (with inhibitors of the renin–angiotensin system, beta-blockers or inhibitors of aldosterone) the so-called "bad" neuroendocrine response. Development of ARNI, on the contrary, has led to consider the neuroendocrine response to HFrEF from a different angle, which is to say that the activation is not always deleterious, but it could also be beneficial. This concept is highlighted by the enhancement of the activity of atrial natriuretic peptide induced by sacubitril/valsartan in the PARADIGM trial, and found as proof from early studies on untreated patients with constrictive pericarditis. The possibility that sacubitril inhibition of neprylisin acts by enhancing substance P and gene-related calcitonin peptide is also considered, as well as the negative effect of neprylisin inhibition. We report here the results of the discussion.

Why PARADIGM-HF is an important trial

PARADIGM-HF established that, in patients with HFrEF and under dual neurohormonal blockade with a beta-blocker and a mineralocorticoid receptor antagonist, the additional combined blockade of neprylisin and angiotensin-II receptor with sacubitril/valsartan is superior to the sole inhibition of the renin–angiotensin axis with an angiotensin converting enzyme inhibitor (ACEI) alone.

This is an important step forward in HFrEF pharmacological therapy for several reasons.

The results of PARADIGM-HF are robust [6]. The benefits of sacubitril/valsartan on outcomes compared to enapril have been clearly demonstrated, including the reduction of the risk of all-cause death, death from cardiovascular causes, and hospitalization for HF. Benefits were consistent across a vast range of risk scores and the treatment effect was greater in patients with higher risk scores. PARADIGM-HF is the trial of the "three first times":

- For the first time a large prospective trial dedicated to CHF has replaced a new drug to a pre-existing one instead of associating it;
- For the first time an approach based on the addition (instead of antagonization) of a neurohormonal substance has proved to be successful in CHF;
- For the first time after the golden age (1990s), a pharmacologic approach has proved to be able to reduce mortality in CHF.

The impact of PARADIGM-HF was so powerful that its results were immediately translated into the European and American Heart Failure guidelines, where sacubitril/valsartan received an indication Class I for the treatment of HF_rEF, even if only with the support of a single trial [1, 2]. Currently, in the European Society of Cardiology Heart Failure guidelines, sacubitril/valsartan represents a second line therapy for HF_rEF because of PARADIGM-HF trial design. However, subsequent studies further expanded our understanding of the relevance of this drug and of the possible different settings of its utilization. These trials explored (directly or indirectly) three directions:

1. shortening the initial phase of titration;
2. anticipating the treatment to the pre discharge period (in case of hospitalized patients); and
3. initiating sacubitril/valsartan without a preliminary assessment of stability on Enalapril in patients naive of anti RAA drugs.

In the TITRATION trial, 498 patients (with a PARADIGM-HF profile) have been randomized to a classic "conservative or condensed" regimen (50 mg twice daily for 2 weeks, 100 mg twice daily for 3 weeks) without any significant difference regarding safety or "therapeutic success" (defined by achievement and maintaining sacubitril/valsartan 200 mg twice daily without dose interruption/down-titration over 12 weeks) [12].

The TRANSITION trial, [13] enrolled 1002 hospitalized patients after they had been stabilized following an acute HF episode. Patients were randomized to initiate sacubitril/valsartan therapy either in the hospital (pre-discharge) or shortly after leaving the hospital (post-discharge). At 10 weeks, more than 86% of patients were receiving sacubitril/valsartan for 2 weeks or longer without interruption and about half of the patients in the study achieved the primary endpoint, which was a target dose of 200 mg of sacubitril/valsartan twice daily within 10 weeks. HF is a serious progressive disease, with 83% of patients hospitalized at least once for an acute HF episode during the course of

their condition. Hospitalization provides an opportunity for physicians to optimize treatment, according to guidelines, to reduce the likelihood of hospital readmission and death.

More recently, the PIONEER-HF [14] trial22 enrolled patients with HFrEF who were hospitalized for acute decompensated HF. After hemodynamic stabilization, 881 patients were randomly assigned to receive sacubitril/valsartan or enalapril. The time-averaged proportional reduction in the NT-proBNP concentration from baseline through weeks 4 and 8 (the primary end point) was significantly greater in the sacubitril/valsartan group compared to the enalapril group. Interestingly, the greater NT-proBNP reduction was evident as early as the first week 22. Considering these three trials together, more than 300 patients naïve of anti RAA drugs have initiated sacubitril/valsartan in the absence of preliminary assessment of stability on Enalapril without any safety concern.

Both these studies reinforce many HF-experts' current view that ARNIs should be considered a first line therapy in the majority of patients with HFrEF together with beta-blockers, reserving therapy with ACEi for those patients with relative hypotension.

In summary, thanks to PARADIGM-HF results a new and very efficacious CHF therapy is today available after about 30 years of unsuccessful research. Remarkably, the beneficial effect of sacubitril/valsartan is greater than that observed in previous landmark placebo-controlled studies examining classical anti-neuroendocrine strategies [15].

So the question is: why does sacubitril/valsartan succeed in improving outcome so convincingly? What is so special in the combination of valsartan with sacubitril to justify these, somehow unexpected, results? Are the results merely linked to its vasodilating effects or is there anything else?

These were the questions raised in Ferrara.

From neurohormonal blockade to neurohormonal modulation

Undoubtedly, the novel aspect of ARNIs is the "chemically orchestrated" addition of sacubitril, an inhibitor of the enzyme neprylisin, to valsartan. This has led to consider the neuroendocrine activation of HFrEF from a totally different angle; the activation is not always deleterious; actually, it could be beneficial. This last concept is highlighted by the enhancement of the activity of natriuretic peptides induced in PARADIGM-HF by sacubitril/valsartan and found as proof in early studies on patients with constrictive pericarditis.

Thus, the new concept is that in HFrEF it is important to modulate, instead of just blocking the neuroendocrine activation. This has far-reaching consequences not limited to natriuretic peptides but also involving other peptides, which are substrates for neprylisin. Understanding these concepts reveals the real conceptual shift in the treatment of HFrEF with ARNIs.

Spotlight on neprylisin (NEP) inhibition: the good

Neutral endopeptidase (NEP) is not new. First discovered in 1973, in the brush border of rabbit-proximal renal tubule microvilli [16], it is a ubiquitous zinc-dependent endopeptidase that cleaves a variety of active peptides. It is expressed in the gut, heart, lung, fibroblast, brain, and other organs where it is coupled with multiple substrates, suggesting an important role in health and disease. Accordingly, NEP has gained interest because of the impressive benefits of combining its inhibition by sacubitril with valsartan in the PARADIGM-HF study [16]. Some of the peptides substrate for NEP are known to play a role in CHF, such as ANP, BNP and CNP (atrial, brain and cell) natriuretic peptides, respectively; angiotensin I, II, and III; endothelin, bradykinin, substance P, CGRP, and arginine vasopressin [16]. It follows that, NEP has become a pharmacological bio-target in CHF and in hypertension, as its inhibition leads to the gradual increase of the plasma concentration of all its substrates, according to the specific affinity. Interestingly, some of these exert beneficial effects, particularly in the context of HF. At a first glance, in HF, the effect of NEP on natriuretic peptides, bradykinin and angiotensin II, is particularly relevant. However, it is likely that other peptides might also play a significant role.

There are, at least, three natriuretic peptides, atrial and B-type peptides (ANP and BNP, respectively) both of cardiac origin, and endothelial cell natriuretic peptide (*CNP*) produced by the endothelial cells [17]. They are all proteolitically cleaved by NEP with different avidities, which is maximal for CNP, intermediate for ANP and low for BNP [18]. This reflects the easiness with which each peptide enters the interior cavity (the Cleft) of NEP where the catalytic process takes place [16]. The shorter tail of CNP and ANP allows quick interaction and optimal positioning in the NEP cleft. This is relevant as the plasma half-lives of both the peptides are between 2 and 4 min, whilst that for BNP is considerably longer, more than 20 min [19]. Differently, the longer tail of the BNP causes a slow entry to the cleft and several clashes that, in turn, result in a non-optimal orientation for the catalytic process [16]. In addition, the cleavage sites for CNP and ANP occur between the amino acids Cys 7 and Phe 8, thus immediately breaking the ring and inactivating the peptide, while that for BNP occurs far from the ring, between the Met 5-Val 6 amino acids, thus making BNP a poor substrate for human NEP [20] (Fig. 1). This is the reason why, under therapy with ARNI, BNP could still be used to monitor the severity of HF and the success of treatment. However, N-Terminal Pro-B-type natriuretic peptide

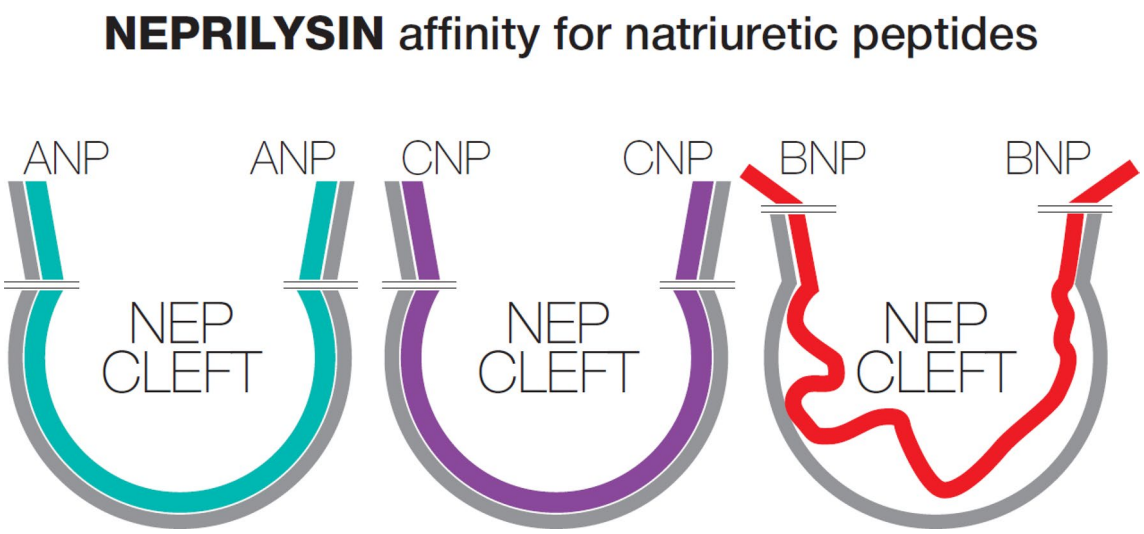

Fig. 1 There are three natriuretic peptides: Atrial (*ANP*), Endothelial (*CNP*), and Brain (*BNP*) natriuretic peptide. They are all cleaved proteolitically by neprylisin (*NEP*) with different affinity CNP > ANP > BNP. This reflects the interaction of each peptide with the interior cavity (*CLEFT*) of NEP

(*NT-Pro BNP*) is not a substrate for NEP; therefore, it seems to be the best biomarker for monitoring the effects of ARNIs.

Bradykinin is also a substrate for NEP as well as for the angiotensin converting enzyme (ACE). Indeed bradykinin exerts beneficial cardio-renal and vasodilator effects besides being a strong anti-apoptotic agent, reducing both myocytes and endothelial cells programmed death [21, 22]. Interestingly, the affinity of NEP for bradykinin is higher than that of ACE [6]. This explains why the combination of NEP with ACE inhibition, by the so-called vasopeptidase inhibitors, with omapatril being the leading agent, when tested in a large randomized clinical trial [23] resulted in an increased occurrence of severe angioedema, overshadowing the benefit on primary endpoint of death and admission to HF. This side effect led to the cessation of vasopeptidase development [24]. Angiotensin-II receptors antagonists, such as valsartan, exert less, if any, effects on bradykinin. Accordingly, in PARADIGM-HF sacubitril/valsartan did not cause significantly higher angioedema than placebo, despite the higher incidence of hypotension [4]. However, it is fair to point out that the construction of PARADIGM protocol with run-in period excluding intolerant patients and the recruitment criteria (few African–American) might have selected patients less prone to angioedema. The results of PIONEER-HF and TRANSITION studies confirm that in an unbiased hospitalized population there is no increase in the rate of angioedema after sacubitril/valsartan [13, 15].

Possible other (*pleiotropic*?) effects of neprylisin

In addition to natriuretic peptides and angiotensin there are other, still understudied, substrates for NEP, which could have contributed to the beneficial effects of PARADIGM-HF. One of these is plasma Calcitonin Gene-Related Peptides (CGRP). This is a group of neuropeptides with widespread distribution in humans and animals, mainly located in the central and peripheral nervous system, the heart, and the vessels [25, 26]. Both the myocytes and the blood vessels have specific receptors for CGRP and their binding from the peptide exerts powerful cardiovascular actions, including non-endothelium dependent vasodilatation, hypotension and a positive inotropic effect [27]. Interestingly, CGRP was found highly activated in 15 patients from India with severe (NYHA class III–IV) untreated HF as well as in European patients with treated HF [27]. Infusion of CGRP in treated and untreated patients with severe HF resulted in a dose–response decrease of systemic and pulmonary resistances and a similar increase of cardiac output without any increase of heart rate or of noradrenaline [28]. The absence of reflex tachycardia in response to the vasodilatation is of particular interest in patients with HF, as it will not increase myocardial oxygen consumption. In healthy volunteers, CGRP increases heart rate, an effect mediated through specific receptors, which increases transmembrane calcium current [29]. However, in the presence of increased catecholamines as in HF, CGRP has the opposite effects and blocks the calcium current of the sinus node [28, 29]. Interestingly, in PARADIGM–HF the vasodilatory effect of Sacubitril/Valsartan did not further increase heart rate, but the majority of the patients were receiving beta-blockers, although not at optimal dose.

Other substrates for NEP, which could count for the cardio-renal effects of NEP inhibition, are endothelin 1 and 3, adreomedullin and vasoactive intestinal polypeptide. All

these peptides have effects theoretically important in HF such as limiting inflammation, reducing smooth muscle contraction, neutrophil adhesion and vascular permeability both in experimental models and in humans [30, 31]. Whether these and other peptides contribute to the impact of NEP inhibition induced by sacubitril remains uncertain and it is worthy of further investigations. NEP inhibition could lead to metabolic, not only strictly hemodynamic, effects. Data from PARADIGM-HF show patients with diabetes at screening who received sacubitril/valsartan had a greater long-term reduction in HbA1c and a lesser probability of initiating insulin than those receiving enalapril.[5]. This is probably mediated by potentiation of glucagon-like peptide-1 (*GLP-1*) receptor signalling. Indeed endogenous GLP-1 and long-acting GLP-1 receptor analogues are degraded not only by dipeptidyl peptidase-4, but also by Neprilysin (Fig. 2).

Spotlight on neprylisin (NEP) inhibition: the bad

As always in nature, there are "the opposites". This is also true for modulation of receptors, of the activity of enzymes, regulatory systems, etc. Indeed, this is true for NEP and it is important to highlight the possible problems related to its inhibition.

An important substrate for NEP is angiotensin II which in HF is overproduced by several enzymes including ACE. As a consequence, plasma angiotensin II in CHF is increased causing vasoconstriction and water retention. It follows that inhibition of NEP further increasing angiotensin II is expected to be deleterious in CHF. This is the reason why it is important to chemically combine sacubitril with valsartan which, at a receptor level, blocks all the negative effects of angiotensin II.

There are other theoretical problems related to NEP inhibition, particularly for the brain where NEP, together with other peptides, degrades endogenous opioids and amyloid-beta peptide [16, 32]. Of notice, NEP inhibitors were originally developed as analgesic in view of the enhancement of brain opioids [33]. This effect, however, resulted rather weak, incomparable with that of morphine and the line of research was interrupted. The affinity of NEP for amyloid-beta peptide is higher than that of opioids and NEP is the leading enzyme for its clearance [34]. This could be a problem as accumulation of amyloid-beta peptide plays a pathologic role for Alzheimer's disease. It follows that, chronic use of NEP inhibitors, particularly those able to cross the brain barriers, might cause or accelerate Alzheimer's disease, particularly in patients with advanced age, like those affected by HF. Experimental data are controversial, showing either an increase of amyloid-beta peptide and amyloid plaque content of the brain in mice after NEP inhibition and in mice transgenic for an amyloid precursor [35, 36] or even a reduction in amyloid plaque [37]. Polymorphisms in NEP gene have been reported to increase the risk of Alzheimer's disease, but other studies show no association [36, 38]. It is also fair to acknowledge that, in contrast with the strategy developed in HF, there is a line of research exploring the possibility of increasing the affinity of NEP for amyloid-beta peptide as a possible therapy for Alzheimer's disease [39].

NEP is involved in neuropeptide degradation and may reduce neurogenic inflammation. Thus, potential side effects of NEP inhibition include increased gut, pancreas, and lung inflammatory activities. The latter may be associated with exacerbation of lung infections, especially in patients exposed to irritants such as tobacco smoking.

Fortunately, none of these theoretical concerns seem to be relevant in humans. The available trials with ARNIs or vasopeptidases inhibitors, with the exception of angioedema, have not reported adverse events of accelerated dementia, or exacerbation of lung and gastrointestinal inflammation. This

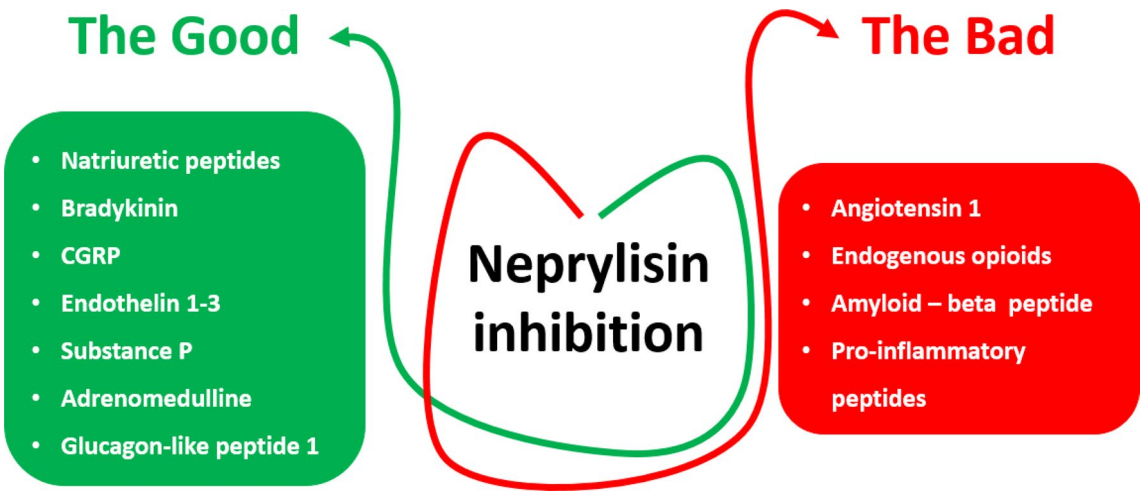

Fig. 2 The good and bad effects of neprylisin inhibition

is reassuring but needs to be verified in "real life" patients, traditionally affected by higher burden of comorbidities than those enrolled in clinical trials. For the risk of exacerbation of Alzheimer's or other more chronic diseases, it is important to perform long-term monitoring of real world patients through carefully planned registries which is one of the next aims of this Italian-Portuguese group (Fig. 2).

Neuroendocrine activation in HF: the good and the bad

The neuroendocrine response to HF is a stereotyped response present in all mammals, reflecting an expression of evolutionary forces to preserve cardiac output and arterial pressure. It is useful during a short time to prevent bleeding and to allow hunting and short stress responses in humans [40]. Conversely, neuroendocrine response becomes deleterious when chronically activated as in HF, when the weakened heart compromises cardiac output and blood pressure. The response is then complex, its intensity being largely determined by the timing, the stage and the severity of the disease and influenced by therapy with diuretics, vasodilators, renin–angiotensin inhibitors, beta-blockers or anti-aldosterone drugs, all of them acting upon neurohormones in many different ways [41–43].

Figures 3 and 4 illustrate, in an over simple manner, the most important systems activated in HF. It is derived from data of previous studies conducted in India, in patients with severe clinical congestive CHF who had never received any therapy in their life [44, 45]. In these untreated patients, arterial pressure was maintained despite the severity of HF [46]. This finding was unexpected as the failing heart is known to cause an increase in venous and a decrease in arterial pressures. The maintenance of arterial pressure resulted to be the consequence of an increase of the systemic resistance, in part due to an increased activity of the sympathetic nervous system and in part due to the activation of the renin–angiotensin–aldosterone system, which increases systemic arterial resistance and retains sodium. Both the systems are activated by the aortic receptors any time that there is a threat to arterial pressure [45]. The negative feedback control of both systems through the blood pressure might explain the great individual variability in plasma concentration of catecholamines, aldosterone and plasma renin activity often found in HF patients [45].

Atria distension, due to the mechanical effect of the cardiac disease and to the expansion of the plasma volume,

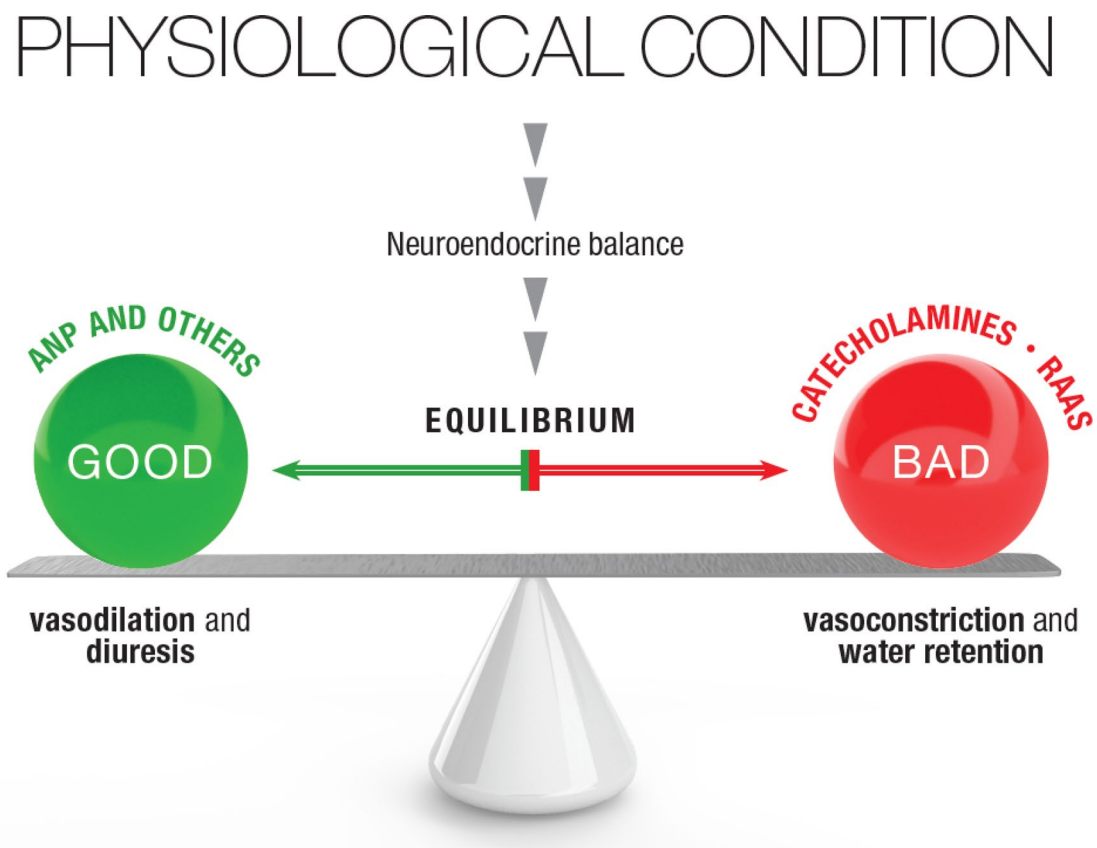

Fig. 3 Under physiological conditions, there is an equilibrium of the neuroendocrine balance

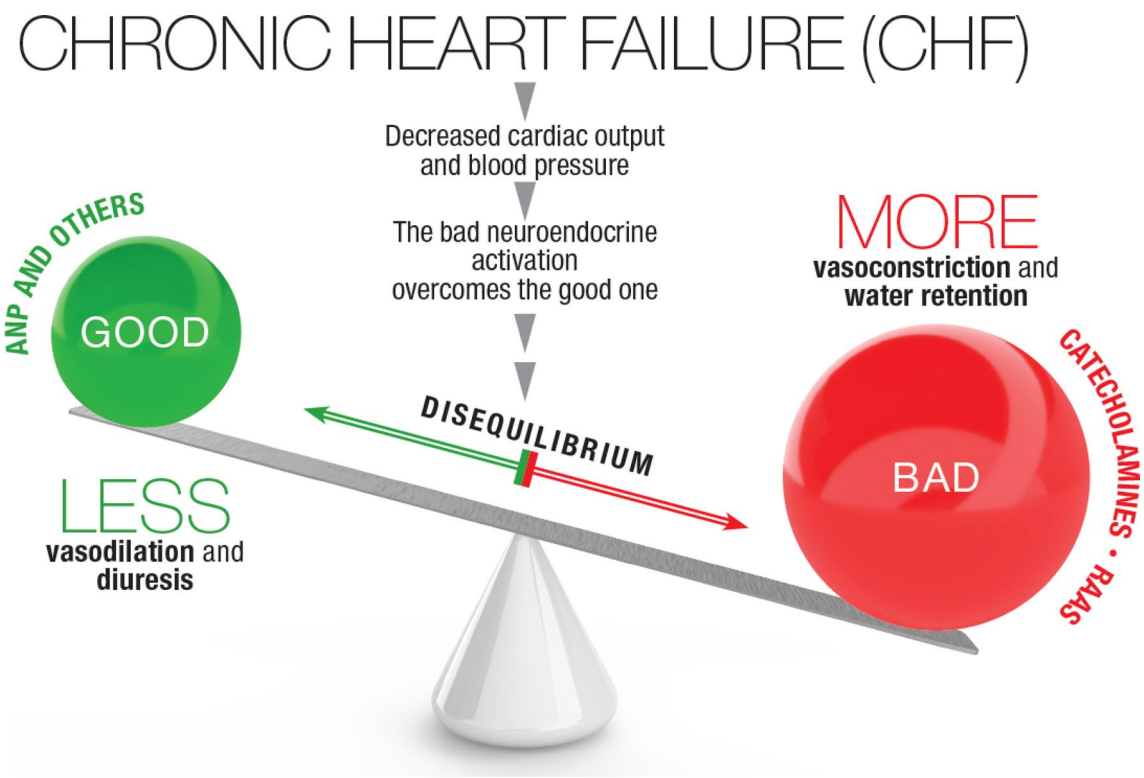

Fig. 4 In the advanced phase of HFrEF, there is a disequilibrium of the neuroendocrine balance. The effects of increased sympathetic and renin–angiotensin activity prevail on those of the atrial and other peptides. As a result, patients are vasoconstrict and retain sodium and water

causes an increased secretion of atrial natriuretic peptides [47]. Our study in untreated patients was performed in the 1990s, before knowledge of other natriuretic peptides, such as BNP or NT-PRO-BNP. The increase of plasma concentration of ANP was, by far, the most striking hormonal response [45].

B-Type natriuretic peptide (BNP) is primarily produced at the ventricular level in response to volume or pressure overload. The ensuing increased end-diastolic pressure leads to myocyte cytoskeletal stretching, triggering a signal-transduction chain reaction that leads to BNP gene expression.

ANP (and BNP) acts via natriuretic peptide G protein-coupled transmembrane receptors activating cyclic guanosine monophosphate (cGMP) as second messenger which, in turn, exerts natriuretic, diuretic and vasodilating action [47]. In addition, natriuretic peptides at cellular levels exert antiapoptotic effect and oppose cardiac hypertrophy and fibrosis, thus exerting anti-remodelling action [48].

These neuroendocrine systems interact extensively.

Natriuretic peptides suppress the activation of the renin–angiotensin–aldosterone and sympathetic nervous systems and, vice versa, beta stimulation causes a release of atrial natriuretic factor [47]. It follows that, in HF two opposite forces are activated: the so-called regulatory systems, leading to vasoconstriction, water retention, hypertrophy, apoptosis and fibrosis, and the so-called *contra-regulatory systems*, leading to vasodilatation and diuresis and having anti-hypertrophic, anti-apoptotic and anti-fibrotic effects.

Once again, even under these pathological circumstances, nature is a dance of opposites: the good and the bad. The equilibrium between this complex, and certainly not exclusive relationship is likely to determine in part, at least, the course of HF in each individual patient. However, eventually, with elapsing time and with the progression of the disease to an advanced phase, the good natriuretic and vasodilatory influences are clearly overwhelmed by the bad ones [45] (Fig. 4).

ARNIs: balancing of the good and the bad neuroendocrine response

The introduction of Sacubitril in the molecule of ARNIs represents a real conceptual change in HF treatment. In the last 30 years, research was directed to identify the bad hormones and to develop ways to block them. Today, the emphasis is to recruit the good hormones, while still blocking the bad ones. The novelty is that sacubitril/valsartan improves the balance of neuroendocrine response to HF in favour of the good one (Figs. 5, 6). At present, it is known that sacubitril/valsartan is enhancing the natriuretic peptides. The BIOMARKER

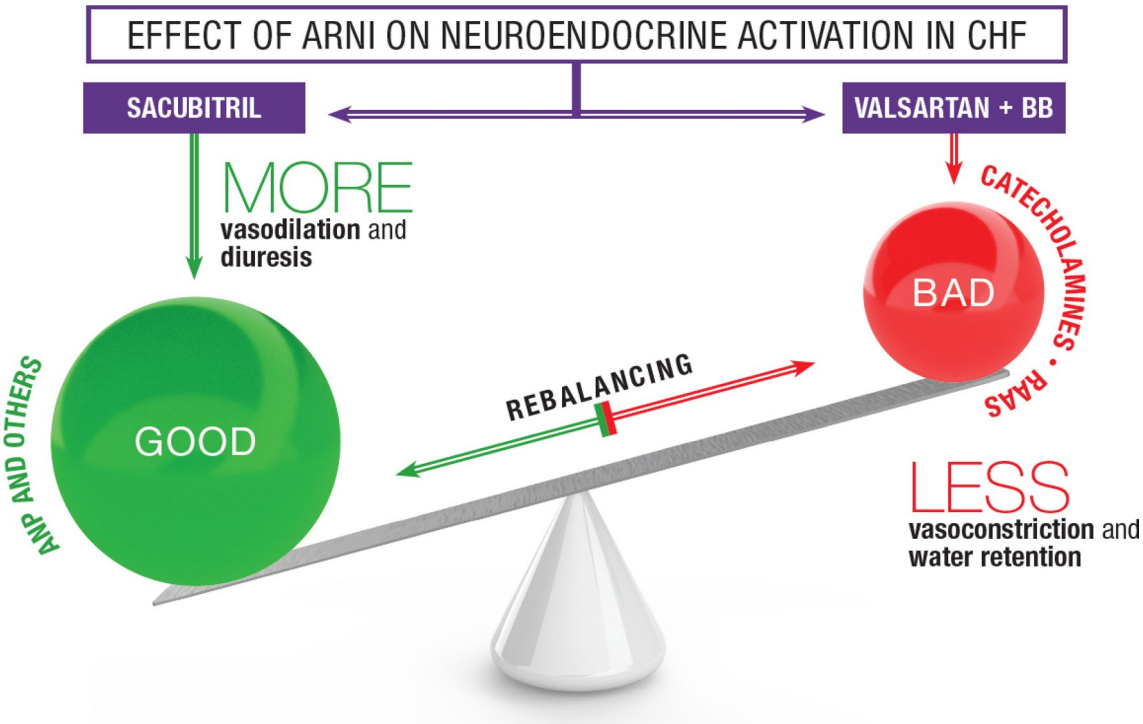

Fig. 5 ARNIs are re-balancing the disequilibrium of the neuroendocrine balance induced by chronic HFrEF. Sacubitril, by inhibiting neprylisin which cleaves ANP and other peptides, increases the viability of ANP, thus promoting physiological dilatation and diuresis and countering the activities of increased sympathetic and renin–angiotensin systems

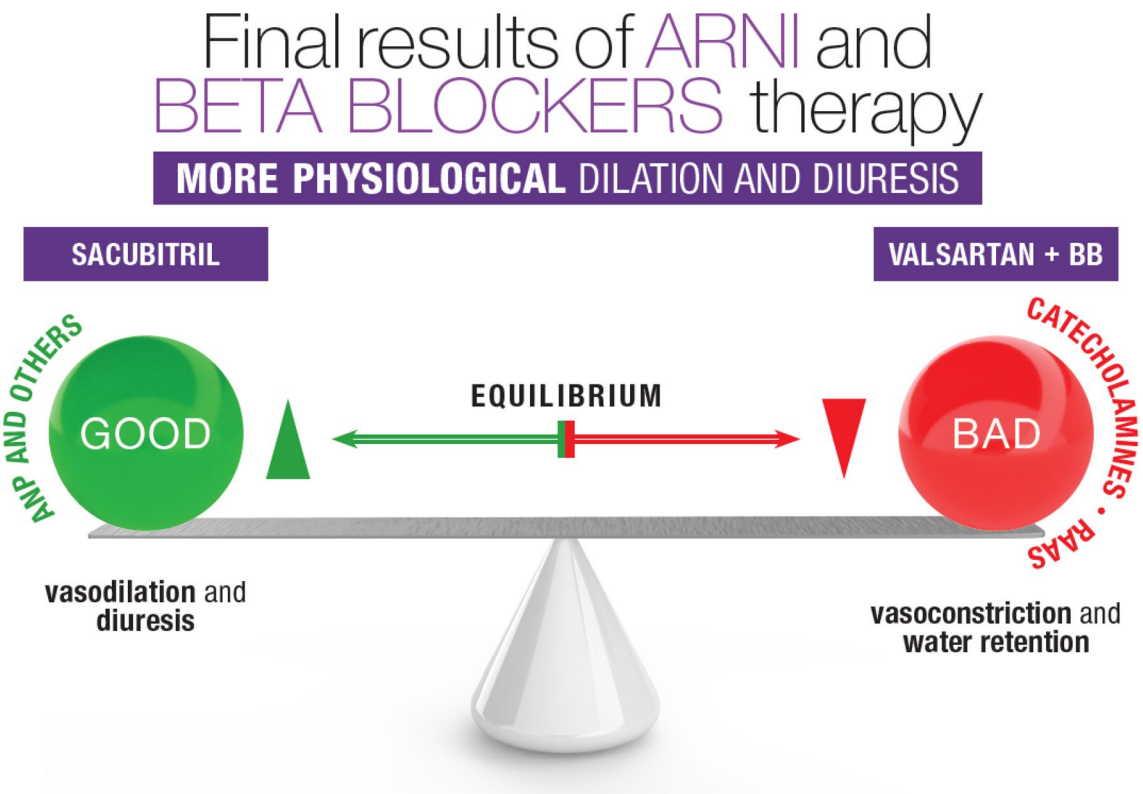

Fig. 6 The final result of sacubitril/valsartan in HF is a re-equilibrium of the neuroendocrine balance due to a physiological increase of diuresis and dilatation

sub-study of the PARADIGM-HF trial showed increased levels of urinary cGMP, the downstream effector of ANP and BNP [49]. Lower plasma levels of NT-proBNP, which is not a substrate of NEP, were observed, reflecting a reduction in ventricular end-diastolic pressure [49]. cGMP, in turn, physiologically increases diuresis and vasodilatation and, counteracts the effects of the bad hormones, improving remodelling.

ARNIs should thus be considered physiological diuretics, and vasodilators but, to some extent and in a provocative way, also RAAS inhibitors and beta-blockers. For this reason, sacubitril/valsartan represents a step forward in HF research and surely will open new, promising ways for further discoveries.

With sacubitril/valsartan a major change occurred in HF therapy; we moved from a neurohormonal blockade strategy to a neurohormonal modulation strategy. Now, we can not only block the regulatory systems, we also can enhance the contra-regulatory systems.

Evidence supporting the relevance of enhancing the contra-regulatory systems is traceable from as early as 1991 and is derived from early studies in patients with constrictive pericarditis.

The case of constrictive pericarditis

Chronic constrictive pericarditis is a rare disease in Western countries, but it is frequent in countries such as India [50]. It is commonly associated with symptoms of advanced HF and with severe retention of sodium and water.

The mechanisms, responsible for the symptoms and salt and water retention in constrictive pericarditis, are different from those in patients with CHF due to myocardial disease. Actually, in constrictive pericarditis, the myocardium and its pumping capacity are normal, so is the glomerular filtration rate of the kidneys. Despite this, the systemic and pulmonary resistances are increased as well as the pulmonary artery wedge pressure and right atrial pressure. Differently from CHF due to myocardial disease, the atrial dimensions are within normal values, as the atria are prevented from expanding by the thick, often calcified, pericardium. As a result, the plasma levels of ANP are increased, but significantly less (*about one third*) than those of patients with CHF due to myocardial disease, while the plasma levels of norepinephrine, renin, aldosterone, and all the other hormones are as high as those of patients with HF due to myocardial disease [50]. The same type of evidence has been later produced on BNP [51]. Indeed, in chronic constrictive pericarditis pericardial constriction, despite high filling pressures, limits the extent of myocardial stretching and the production of natriuretic peptides also at myocardial ventricular level. These findings underline the important role played by ANP in effectively, directly or indirectly, counteracting sympathetic and renin–angiotensin–aldosterone systems activation. In the presence of lower levels of ANP than in CHF due to myocardial disease, the bad hormones take over immediately resulting in high peripheral resistance despite a normal heart function. It follows that, constrictive pericarditis imposes a unique impediment on the circulation. The diminished distensibility of the heart specifically reduces the filling of the ventricles and, thereby, cardiac output. Decreased cardiac output decreases arterial pressure and, thereby, induces the stimulation of the sympathetic nervous system and the renin–angiotensin–aldosterone system [39] in the same way as it occurs with myocardial or valvular disease. However, the constrictive process, at the level of the atria, also prevents adequate release of ANP and, thus, reducing the extent of natriuresis and diuresis induced by that hormone.

Pericardiectomy restores normal haemodynamics and a consequent decrease of plasma concentration of catecholamines, aldosterone, and renin activity occurs. ANP, first, slightly increases and thereafter decreases [43]. In our untreated patients, the return of neurohormones and haemodynamics to a normal status was accompanied by a massive loss of extracellular water and sodium and a substantial symptomatic improvement.

We believe that Constritive Pericarditis provides evidence of the importance of ANP in counteracting the activation of the pathways involved in the pathogenesis of HF and in the development of symptoms and of sodium and water retention. This fact reinforces the notion that, at least, some of the clinical benefits induced by sacubitril/valsartan are due to a better balance between the good and the bad of neuroendocrine response to HF. In accordance, the infusion of ANP in untreated patients with CHF due to myocardial disease caused significant natriuresis and diuresis but, unfortunately, also several side effects, most likely because it was synthetic and not a "physiological" ANP.

Conclusions

The emergence of sacubitril/valsartan represents the advent of a new strategy for treating CHF. Its beneficial effects are related in part, at least, to a positive modulation of the neuroendocrine response to the disease. This represents a shift in HF medical therapy, which was directed to counteract the "bad" hormones with ACEis, angiotensin-II inhibitors, antialdosterone drugs, and beta-blockers. Sacubitril/valsartan stimulates the "good" and blocks the "bad" neuroendocrine responses and, in doing so, reinstates a more physiological neuroendocrine balance resulting in an improvement of diuresis, a reduction of peripheral resistances and blood pressure, and an amelioration of the symptoms.

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Compliance with ethical standards

Conflict of interest RF has received honoraria for steering committee membership and consulting from Novartis and Servier; and speaker fees from Cipla, Lupin, Merck Serono, and Servier International. JC has consulted and received speaker fees, or investigational grants for Abbott, AstraZeneca Pharmaceuticals, Bial, Boehringer Ingelheim, Menarini, Merck Serono, Merck Sharp & Dohme, Novartis, Orion, Pfizer, Sanofi and Vifor M.C.F. has received fees from Novartis, Servier,Orion, Roche, Bayer and Vifor (companies that develop and market tests and/or treatments in the area of HF) for HF consulting, sitting on clinical study steering committees and giving lectures at congresses and other scientific sessions. CA has received lecture fees and honoraria for consultancy from Novartis and Servier. JIM has no conflict of interest. DM has no conflict of interest. CR has received honoraria (as a speaker and board member) from Novartis.

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