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Heart failure

Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure

Thomas H. Langenickel[1], William P. Dole[2,*]

[1]Translational Medicine, Novartis Pharma AG, Basel, Switzerland
[2]Novartis Institutes for Biomedical Research Inc., 100 Technology Square, 1650 B, Cambridge, MA 01239 USA

The natriuretic peptide system exerts beneficial cardiorenal effects in chronic heart failure, whereas activation of the renin–angiotensin–aldosterone system exerts opposing and deleterious effects. LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, targets both neurohormonal systems by inhibiting neprilysin, which prevents natriuretic peptide degradation, while concomitantly blocking the angiotensin (AT_1) receptor. In clinical studies of patients with chronic heart failure with reduced and preserved left ventricular ejection fraction, LCZ696 has been shown to improve biomarkers of cardiorenal function. The effects of LCZ696 on cardiovascular outcomes and survival in patients with heart failure are currently being investigated.

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Robert Willette – Heart Failure Drug Discovery Performance Unit, GSK Pharmaceuticals, King of Prussia, USA.

Introduction

Heart failure (HF) is a common syndrome, resulting in high mortality. The prevalence of HF has risen steadily in recent years and this trend is expected to continue due to a growing aging population with more cardiovascular risk factors [1,2]. Indeed, risk factors, such as hypertension, are common prognostic comorbidities in chronic HF [3].

The impact of HF on patient quality of life and the financial burden imposed on the healthcare system are great, with frequent costly hospitalizations and a 5-year mortality rate of approximately 50% [2]. While survival rates have improved for HF with reduced ejection fraction (HFrEF) due to more widespread use of drugs that block the renin–angiotensin–aldosterone system (RAAS) residual mortality rates remain high. For patients with HF with preserved ejection fraction (HFpEF) no therapy has proven to be effective at reducing morbidity and mortality [4]. Consequently, there is an urgent need for new therapies to prevent and treat HFrEF and HFpEF.

Role of the RAAS and natriuretic peptides (NPs) in heart failure

The consequences of activation of the RAAS and sympathetic nervous system in the pathogenesis of HF are well established, as is the therapeutic benefit of RAAS blockers in improving HF

*Corresponding author.: W.P. Dole (bill.dole@novartis.com)

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outcomes. A growing body of experimental and clinical evidence indicates that the natriuretic peptide (NP) system, which mediates beneficial cardiorenal effects, is also impaired in HF [5]. This suggests that approaches designed to upregulate NPs and/or enhance their biological activity may be of therapeutic benefit, particularly in conjunction with RAAS blockade [5].

The RAAS and HF

Chronic HF is a progressive condition characterized by elevated cardiac filling pressures, reduced cardiac output and decreased tissue oxygen delivery [6]. These hemodynamic abnormalities result in activation of the RAAS and sympathetic nervous system to maintain vital organ perfusion [6]. Initially, this serves as an acute compensatory response, but prolonged activation contributes to the pathophysiology of HF, resulting in progressive cardiorenal abnormalities, including myocardial hypertrophy, fibrosis and apoptosis, increased systemic vascular resistance, and increased sodium and water retention [6,7].

The NP system and HF

The NP system comprises three structurally similar peptides with cardiorenal protective properties: atrial NP (ANP), B-type NP (BNP) and C-type NP (CNP) [8]. ANP and BNP are primarily expressed in the heart and released by cardiomyocytes in response to mechanical stretch [5]. CNP is derived mainly from endothelial and renal cells and secreted in response to endothelium-dependent agonists and pro-inflammatory cytokines [5]. As filling pressures rise in HF, increased cardiac stretch causes the secretion of precursor NPs, which are cleaved by specific proteases to produce biologically active NPs which then act on NP receptors (NP receptor-A [NPR-A], NPR-B and NPR-C) [8]. Binding of NPs to NPR-A and NPR-B activates particulate guanylate cyclase resulting in increases in the second messenger, cyclic guanosine monophosphate (cGMP), which mediates many of the cardiovascular and renal effects of the NPs [8,9].

NPs are cleared from the circulation by two mechanisms – binding to NPR-C and inactivation (hydrolytic cleavage) by neprilysin [8]. Neprilysin has a high affinity for both ANP and CNP, and a lower affinity for BNP, which is more resistant to hydrolysis [10]. Since neprilysin does not hydrolyze N-terminal pro-BNP (NT-proBNP) [11], it remains a useful cardiac biomarker to assess therapeutic effect and prognosis in patients treated with neprilysin inhibitors.

The cardiovascular and renal effects of the NP system oppose those of the RAAS [12], providing the scientific and therapeutic basis for neprilysin inhibition in the setting of HF. One of the major effects of NPs is vasodilation, which results from cGMP-mediated relaxation of smooth muscle cells as well as indirect effects of NPs to inhibit the RAAS and decrease endothelin-1 (ET-1) production [9]. Indeed, NPs have been shown to cause significant reductions in systemic vascular resistance, pulmonary artery pressure, pulmonary capillary wedge pressure and right arterial pressure in patients with severe HF [13]. NPs also mediate other beneficial hemodynamic effects, including reducing arterial stiffness and enhancing endothelial function [14].

NPs promote sodium and water excretion by inhibiting sodium reabsorption in the proximal and distal nephron, while preventing decreases in glomerular filtration rate by regulating tubuloglomerular feedback [9]. These effects of NPs have been observed in patients with severe HF, resulting in improvement in hemodynamics and renal function [13]. In addition to the direct effects of NPs on the kidney, their inhibitory actions on the RAAS and sympathetic nervous system also contribute to their natriuretic, diuretic and hemodynamic effects [9,14].

The NPs have potent cardiac antihypertrophic and antifibrotic properties. In animal models, ANP and CNP inhibit cardiac hypertrophy induced by angiotensin II (Ang II) or ET-1 [15,16]. Furthermore, in cardiac fibroblasts, ANP and BNP inhibit the fibrotic effects of transforming growth factor beta (TGF-β), while Ang II-induced interstitial fibrosis was inhibited by CNP [16].

Recent experimental and clinical data indicate that NPs have physiologically important metabolic effects that may be relevant to HF [17,18]. ANP has been shown to stimulate lipolysis in human adipocytes by activating the NPR-A receptor and increasing intracellular cGMP [19]. ANP-induced lipolysis could contribute to cardiac energy utilization by providing substrate in the form of free fatty acids and promoting lipid oxidation through increased mitochondrial biogenesis [17,20]. On the other hand, an imbalance between fatty acid uptake and utilization for adenosine triphosphate (ATP) generation could result in mitochondrial oxidative stress and lead to excessive cardiomyocyte accumulation of neutral lipids, contractile dysfunction and lipotoxicity [21]. Other metabolic effects of NPs demonstrated in human tissue samples include increased oxygen consumption and enhanced expression of adiponectin. Studies in animal and human adipocytes have also shown that NPs induce brown fat thermogenesis and can mediate a phenotypic switch from white to brown fat [17]. Furthermore, there is emerging evidence that NP signaling may directly improve glucose control and inhibit adipocyte growth [17,18,22]. Finally, a specific human ANP genetic polymorphism which increases circulating ANP has been reported to protect against hypertension and metabolic syndrome [23]. The relevance of the metabolic effects of NP to insulin resistance and cardiovascular diseases is an active area of research.

Dysregulation of the NP system and role of neprilysin in HF

While it was initially thought that the NP system was upregulated in HF due to high circulating levels of total

immunoreactive ANP and BNP, recent studies indicate that mature BNP (BNP1–32) levels are reduced and levels of less biologically active BNP fragments are increased [5]. This is due to altered processing of proBNP to biologically active BNP1–32 [24] and partly explains the blunting of the physiological response to high levels of total immunoreactive BNP observed in patients with HF [5]. Thus, advanced HF may represent a state of NP deficiency [5]. Furthermore, the expression and activation of neprilysin are increased in patients with HF, which enhances the rate of degradation of NPs and contributes to reduced levels of biologically active NPs [25].

As HF progresses, relative resistance or hyporesponsiveness to NPs develops, which is particularly evident in the kidney and vasculature [8,12]. This hyporesponsiveness is an important feature of HF that adversely affects prognosis by worsening sodium retention and volume overload and increasing peripheral vascular resistance. The mechanisms for NP resistance are multifactorial and include: downregulation of NP receptors, dysregulated NP signal transduction, increased cGMP degradation and activation of the RAAS [26].

In addition to hydrolyzing the NPs, neprilysin also hydrolyzes other vasoactive peptides, including substance P, bradykinin, ET-1, angiotensin I (Ang I) and Ang II [27,28]. Since there are multiple neprilysin substrates with differing and, in some instances, opposing biologic actions, the pharmacologic profile of neprilysin inhibitors is complex and will depend on the net effect on all biologically relevant substrates. While inhibition of neprilysin is expected to result in beneficial cardiovascular and renal effects in HF by increasing NP levels, corresponding increases in Ang II and ET-1, both of which have vasoconstrictor, pro-fibrotic and pro-hypertrophic properties, would be expected to oppose the beneficial effects of the NPs. In the case of angiotensin, neprilysin hydrolyzes and inactivates Ang II; therefore, neprilysin inhibition alone will not only increase NP levels but can also result in accumulation of Ang II, which could attenuate or negate any beneficial NP effects in the setting of HF. The increase in Ang II observed with neprilysin inhibition provides a rationale for concomitant RAAS blockade. However, neprilysin also converts Ang I to Ang 1–7 [28], which has vasodilating, antiproliferative and natriuretic actions mediated through activation of the Mas receptor [29]. In the case of ET-1, neprilysin not only hydrolyzes ET-1, but also its precursor peptide big ET-1. Thus, the effect of a neprilysin inhibitor on ET-1 levels will depend on the net effect of hydrolysis of both big-ET1 and ET-1 [27]. It should also be noted that both substance P and bradykinin, which are both inactivated by neprilysin, have vasodilatory properties, increase vascular permeability and, when combined with an angiotensin-converting-enzyme inhibitor (ACEI), are implicated in the pathogenesis of angioedema [30], a potential side effect of neprilysin inhibitors.

NPs as treatment for chronic HF

The therapeutic rationale for the initial development of neprilysin inhibitors as a potential treatment for chronic HF is based on the observation that neprilysin inhibition increases endogenous NP levels [31,32]. One of the first selective neprilysin inhibitors studied in humans was candoxatril, which produced beneficial hemodynamic, natriuretic and diuretic effects in patients with chronic HF [32,33]. In patients with chronic HF receiving ACEI, candoxatril also improved exercise tolerance compared with placebo [34].

However, as noted above, neprilysin also degrades Ang II; therefore, neprilysin inhibition also activates Ang II-dependent pathways [31], limiting the utility of selective neprilysin inhibitors as monotherapy for HF. Activation of the RAAS attenuates the actions of NPs and RAAS inhibition has been reported to potentiate the effects of neprilysin inhibition in a canine model of HF [35]. Therefore, achieving the potential clinical benefits of neprilysin inhibition will likely require concomitant inhibition of the RAAS.

These observations led to the therapeutic strategy of concomitant inhibition of neprilysin and the angiotensin-converting enzyme (ACE), and to the development of omapatrilat. In a Phase III trial in patients with chronic HF, omapatrilat demonstrated a trend towards improved morbidity and mortality with once daily dosing that might have been even greater with a more frequent dosing regimen [36]. However, omapatrilat treatment was also associated with a substantially increased risk of angioedema [36], and its development was discontinued.

Angioedema is thought to be mediated by increases in bradykinin, des-Arg9-bradykinin and possibly substance P, potent vasoactive peptides that cause vasodilation and enhance vascular permeability [30]. Bradykinin is degraded predominantly by ACE, but also by aminopeptidase P (APP), neprilysin and dipeptidyl peptidase 4 (DPP-4) [37]. Compared with ACE and aminopeptidase P, the relative contribution of neprilysin to the degradation of substance P and bradykinin appears to be very small [37]. In the presence of ACE inhibition, the development of angioedema is believed to require functional (genetic or pharmacologic) defects in several non-kininase II enzymatic pathways [30,38]. Omapatrilat not only inhibits ACE, but also inhibits APP and neprilysin. The increase in bradykinin resulting from inhibition of all three enzymes may have been the cause of the increased incidence of angioedema observed with that agent [37].

The therapeutic strategy of concomitant neprilysin and RAAS inhibition still holds promise for patients with chronic HF assuming the risk of angioedema can be minimized while achieving superior efficacy compared to RAAS blockers alone. While angiotensin type 1 (AT_1) receptor blockers (ARBs) are known to cause angioedema, the reported incidence is much less than that for ACEIs [39]. The proposed mechanism for ARB induced angioedema involves Ang-II/AT_2 receptor

mediated increases in bradykinin due to weak indirect inhibitory effects on ACE and possibly neprilysin [40]. Thus, a potentially more successful therapeutic strategy would be to block the RAAS at the AT_1 receptor rather than inhibit ACE. Experiments in stroke-prone spontaneously hypertensive rats have shown that concomitant neprilysin inhibition and AT_1 receptor blockade improved endothelial function to a similar extent as that achieved with combined neprilysin and ACE inhibition [41]. In an *in vitro* study in rat cardiomyocytes and fibroblasts, simultaneous addition of a neprilysin inhibitor and ARB into the culture media was more effective than the ARB alone in inhibiting biochemical markers of cardiac hypertrophy and fibrosis [42]. Finally, an *in vivo* study in spontaneously hypertensive rats found that concomitant neprilysin inhibition and angiotensin receptor blockade lowered blood pressure (BP) to a similar extent as neprilysin-ACE inhibition with omapatrilat, but had no effect on tracheal plasma extravasation (a bradykinin-dependent surrogate for upper airway angioedema), whereas neprilysin-ACE inhibition with omapatrilat increased tracheal plasma extravasation [43]. These experimental data highlight the potential for concomitant neprilysin inhibition and AT_1 receptor blockade for producing beneficial cardiovascular effects without increasing the risk of angioedema.

LCZ696, a novel angiotensin receptor neprilysin inhibitor (ARNI): pharmacological profile, experimental and clinical results

ARNIs represent a novel class of drugs being developed for the treatment of HF whose multimodal mode of action involves neprilysin inhibition and AT_1 receptor blockade. ARNIs enhance the beneficial physiological response of NPs while blocking the harmful effects of RAAS activation (Fig. 1).

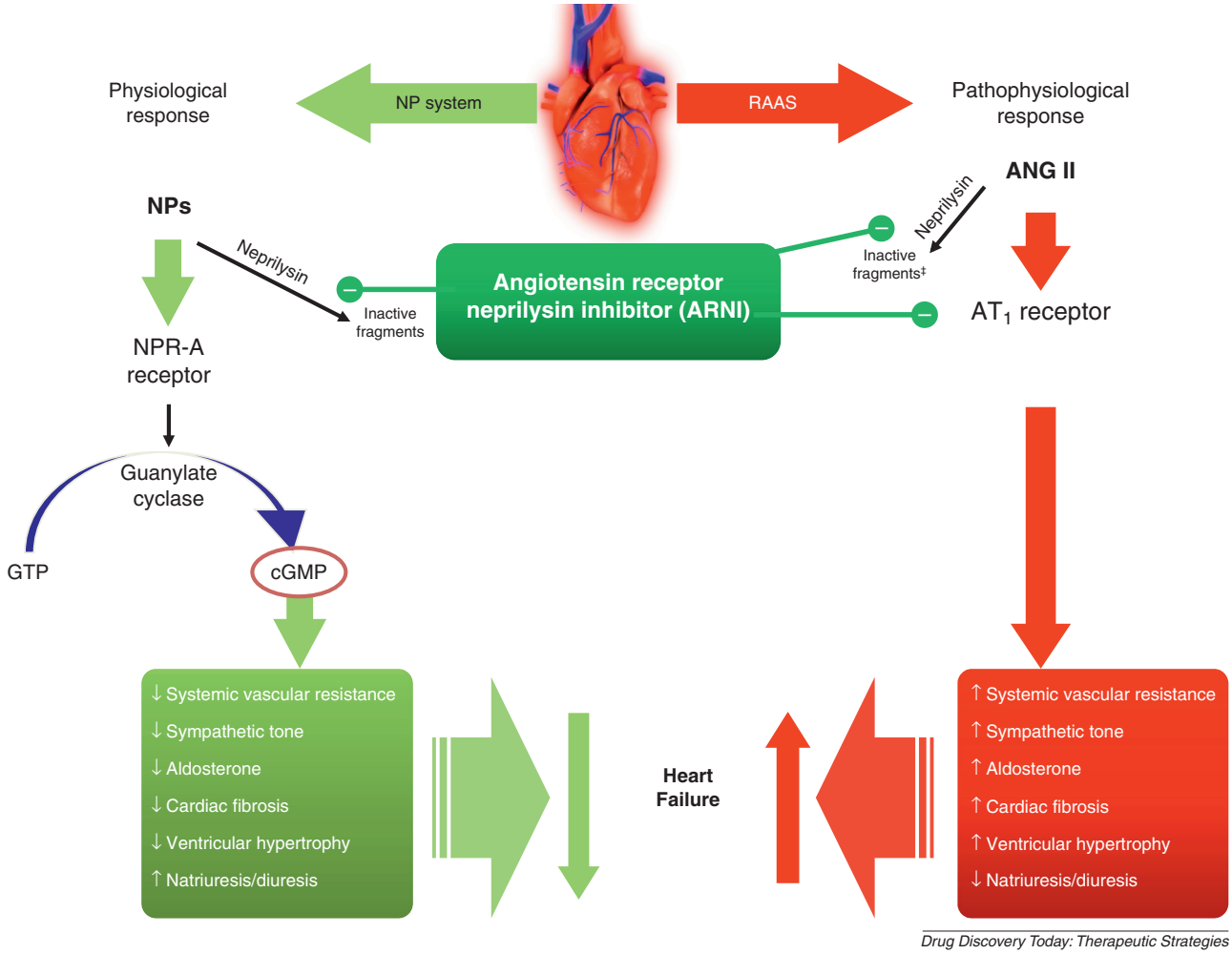

Figure 1. Angiotensin receptor neprilysin inhibitors have the potential to modulate two counter-regulatory neurohormonal systems in HF: the renin–angiotensin–aldosterone system and natriuretic peptide system [6,8,12,27]. ANG: angiotensin; ARNI: angiotensin receptor neprilysin inhibitors; AT_1: angiotensin type 1; cGMP: cyclic guanosine monophosphate; GTP: guanosine-5′-triphosphate; HF: heart failure; NP: natriuretic peptide (e.g. atrial natriuretic peptide [ANP], B-type natriuretic peptide [BNP], etc.); NPR-A: NP receptor-A; RAAS: renin–angiotensin–aldosterone system; ‡*In vitro* evidence.

Pharmacokinetic and pharmacodynamic profile of LCZ696

LCZ696 is the first in class ARNI in clinical development. LCZ696 is a new chemical entity comprising anionic moieties of the neprilysin inhibitor prodrug AHU377 and the ARB valsartan [44]. Oral administration of LCZ696 provides concomitant systemic exposure to AHU377, which is metabolized to the active neprilysin inhibitor LBQ657, and valsartan [45].

The pharmacokinetics of LCZ696 have been well characterized. Oral administration of single and multiple ascending doses of LCZ696 to 41 healthy volunteers resulted in rapid, approximately dose proportional systemic exposure to both the ARB and neprilysin inhibitor moieties of LCZ696 [45]. Following multiple dose administration, the systemic exposures of valsartan and the active neprilysin inhibitor LBQ657 occurred rapidly, with maximum plasma concentration (C_{max}) for valsartan achieved within 1.6–4.9 hours, and for LBQ657 within 1.8–2.7 hours [45].

Experimental studies have demonstrated that LCZ696 inhibits both neprilysin and the RAAS. Sprague–Dawley rats infused with ANP (450 ng/kg/min) exhibited a dose-dependent augmentation of plasma ANP immunoreactivity in response to LCZ696, indicating neprilysin inhibition (Fig. 2). The antihypertensive effects of LCZ696 were studied in conscious chronically instrumented double transgenic rats expressing the genes for human renin and angiotensinogen [45]. In this model of Ang-II-induced hypertension, oral administration of LCZ696 resulted in a dose-dependent and long-lasting reduction in mean arterial pressure (Fig. 2).

A study in healthy human subjects confirmed that LCZ696 provides concurrent neprilysin inhibition and AT_1 receptor blockade [45]. Following multiple dose administration of LCZ696, 24-hour mean plasma cGMP (the NP effector signaling messenger) was increased compared with placebo, which is consistent with neprilysin inhibition. Dose-dependent increases in plasma cGMP compared with placebo were observed as early as 4 hours post-dose, with levels returning to baseline by 24 hours (Fig. 3; [45]). LCZ696 also resulted in dose-dependent increases in plasma renin concentration, plasma renin activity (PRA) and Ang II levels, which is consistent with AT_1 receptor blockade (Fig. 3; [45]). The maximum concentrations of the RAAS biomarkers were reached by 4 hours after administration of multiple doses of LCZ696. Furthermore, the sustained pharmacodynamic effects following LCZ696 administration, together with the long observed plasma $t_{1/2}$ for both valsartan and LBQ657, indicate the suitability of LCZ696 for once- or twice-daily dosing.

LCZ696 pharmacodynamics, clinical efficacy and safety in patients with hypertension

A study in patients with hypertension (mean systolic BP 139.6 ± 9.2 (standard error) mmHg at baseline) has examined the effect of LCZ696 compared with valsartan on natriuresis, diuresis and urinary cGMP [46]. LCZ696 (400 mg once daily for 7 days) was associated with increases in natriuresis, diuresis and fractional sodium excretion compared with valsartan. For each of these measures, the natriuretic effect of LCZ696 was greatest on the first day of drug administration and diminished with continued dosing, likely

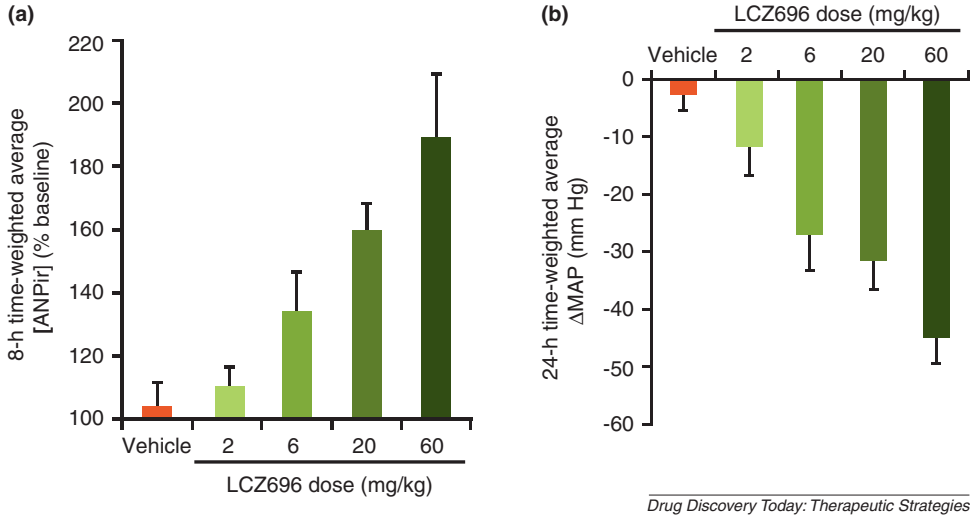

Figure 2. Effect of oral administration of LCZ696 on **(a)** change from baseline in plasma atrial natriuretic peptide immunoreactivity (ANPir) in Sprague-Dawley rats (n = 4) infused with ANP (450 ng/kg/min); **(b)** change in mean arterial pressure (ΔMAP) in double-transgenic rats (dTGR) (n = 6) overexpressing human renin and angiotensin and exhibiting angiotensin II-dependent hypertension [45]. ANP: atrial natriuretic peptide; ANPir: atrial natriuretic peptide immunoreactivity; dTGR: double-transgenic rats; MAP: mean arterial pressure. This material is reproduced with permission of John Wiley & Sons, Inc. Copyright 2010 John Wiley & Sons, Inc.

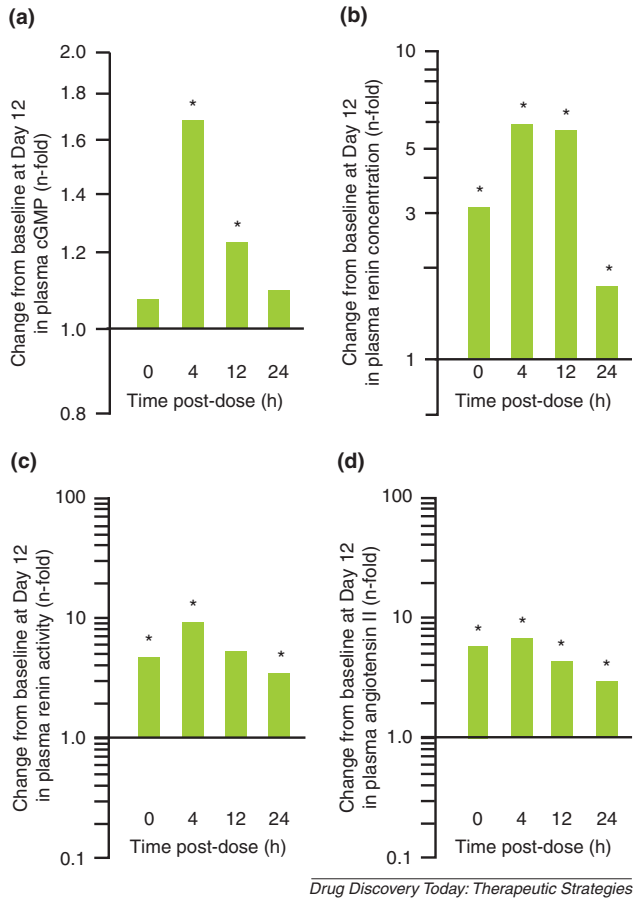

Figure 3. Effect of oral administration of LCZ696 200 mg on **(a)** geometric mean change in plasma cGMP; **(b)** renin concentration; **(c)** plasma renin activity; **(d)** angiotensin II in healthy volunteers ($n = 42$) [45]. NB: In this dose-escalation study, patients received multiple doses of LCZ696 (50, 200, 600 and 900 mg). Data shown are for the 200 mg dose, which gave the greatest increase in cGMP. *$p < 0.05$ versus placebo. cGMP: cyclic guanosine monophosphate.

due to counter-regulatory mechanisms in response to the cumulative negative sodium balance. The study also showed that LCZ696 provided sustained neprilysin inhibition as indicated by increased urinary cGMP excretion throughout the study [46]. Treatment with LCZ696 in this study was further associated with larger reductions in both systolic BP and diastolic BP compared with valsartan. The clinical efficacy of LCZ696 has also been studied in a randomized, double-blind, placebo-controlled study in 1328 patients with mild-to-moderate hypertension [47]. LCZ96 (200 and 400 mg) provided significantly greater BP reductions than comparable exposure to valsartan (160 mg and 320 mg, respectively). LCZ696 was well tolerated, with no reported cases of angioedema and no serious adverse events judged to be related to LCZ696 [47]. A study in Asian patients with mild-to-moderate hypertension has confirmed the BP-lowering effect and favorable safety profile of LCZ696 [48].

LCZ696 pharmacodynamics, clinical efficacy and safety in patients with HFrEF

LCZ696 has been studied in patients with HFrEF. In an open-label, non-controlled study of 30 patients with stable chronic HF and left ventricular ejection fraction (LVEF) ≤40%, LCZ696 100 mg titrated to 200 mg twice daily was shown to increase plasma cGMP and urinary ANP after 7 and 21 days of drug administration, confirming inhibition of neprilysin [49]. Furthermore, administration of LCZ696 led to significant increases in PRA and plasma renin concentration, indicative of AT_1 receptor blockade. In addition, plasma aldosterone and ET-1 levels were reduced, confirming clinically relevant RAAS inhibition [50]. Importantly, LCZ696 significantly decreased plasma NT-proBNP ($p < 0.001$) [49]. No serious adverse events occurred during the study. These effects support further studies of LCZ696 in chronic HF.

LCZ696 is currently being investigated in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF), a Phase III randomized, double-blind, parallel-group study comparing the long-term safety and efficacy of LCZ696 versus enalapril in patients with chronic HF and reduced LVEF (≤40%). The primary endpoint is the composite of cardiovascular death or HF hospitalization. The secondary endpoints include assessment of changes in HF symptoms, physical limitations on quality of life, new onset of atrial fibrillation, and development/progression of renal dysfunction [51]. PARADIGM-HF is an event-driven trial and, as of January 17, 2013, the study is fully enrolled, with 8436 randomized patients at 985 centers in 47 countries [51].

LCZ696 pharmacodynamics, clinical efficacy and safety in patients with HFpEF

LCZ696 has also been investigated in patients with HFpEF. HFpEF is characterized by abnormal left ventricular diastolic function with associated increases in ventricular filling pressures, increased vascular stiffness and impairments in systolic function despite preserved ejection fraction [52]. HFpEF is associated with an impaired NP response and renal endocrine response to volume overload [52]. As a result, it is hypothesized that LCZ696, by augmenting the effects of NPs, would be of clinical benefit in these patients.

PARAMOUNT was a Phase II, randomized, double-blind multicenter trial in patients with HFpEF (LVEF ≥45%) [52]. The primary endpoint was change from baseline to Week 12 in levels of NT-proBNP [52], a marker of left ventricular wall stress that is associated with adverse outcomes in patients with HFpEF [53]. Patients were randomized to receive LCZ696 200 mg twice daily or valsartan 160 mg twice daily (dose equivalent) for 36 weeks. At 12 weeks, LCZ696 reduced NT-proBNP from baseline by 23% compared with valsartan ($p = 0.005$; Fig. 4). PARAMOUNT also assessed the effect of LCZ696 on left atrial structure and function by measuring left

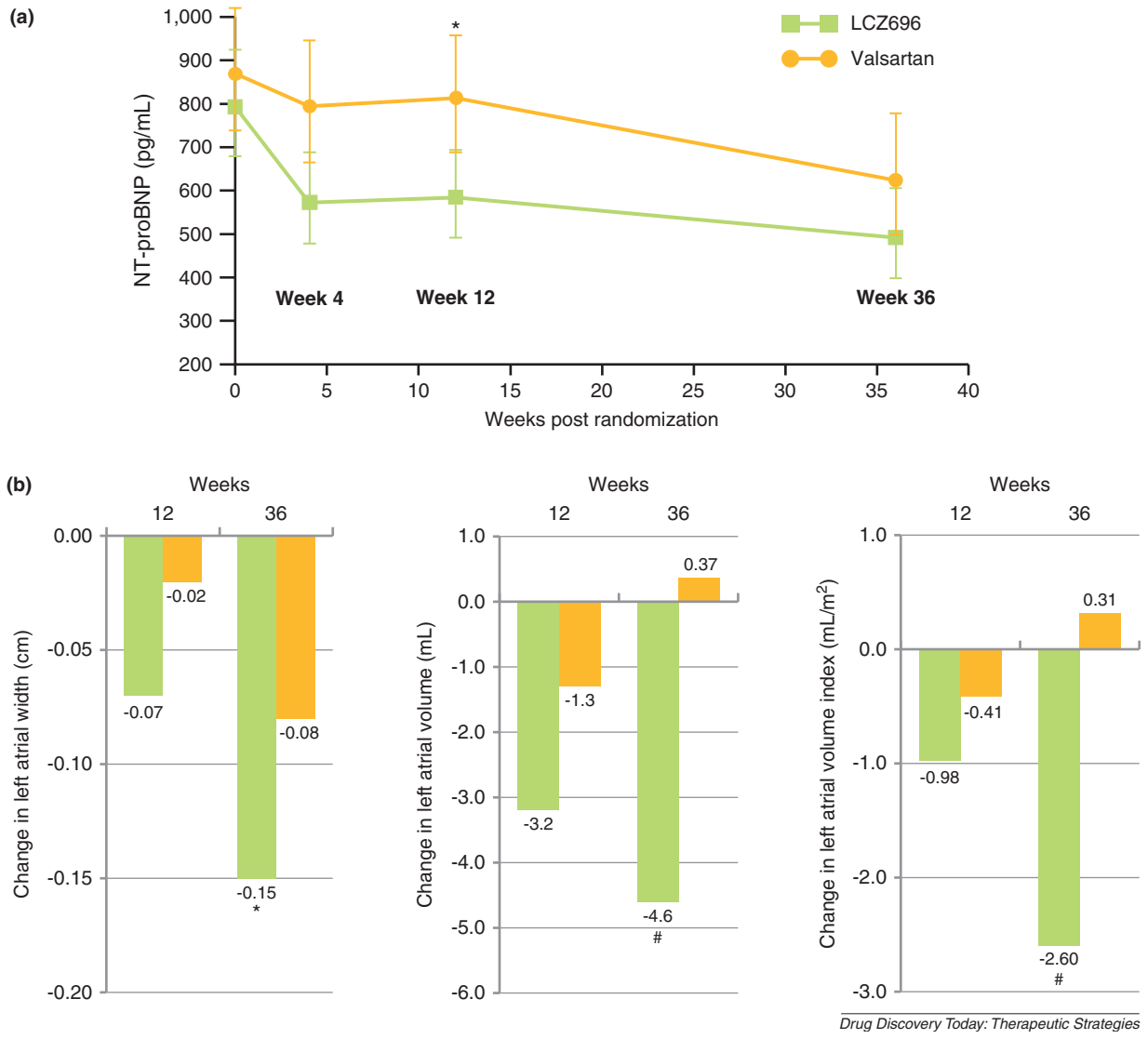

Figure 4. Effect of LCZ696 200 mg twice daily versus valsartan 160 mg twice daily (dose equivalent) in patients with chronic HF with preserved ejection fraction (NYHA class II–III, LVEF ≥45%, NT-proBNP >400 pg/mL). **(a)** NT-proBNP concentration (pg/mL) (geometric mean [95% CI]); **(b)** left atrial width, volume and volume index (mean SD) [52]. *p = 0.005; #$p < 0.01$ versus valsartan. CI: confidence interval; HF: heart failure; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; SD: standard deviation.

atrial width, volume and volume index [52], parameters that have been shown to be predictors of outcome in chronic HF, with and without reduced LVEF [54,55]. After 36 weeks of treatment, left atrial width, volume, and volume index were significantly reduced from baseline to a greater extent with LCZ696 compared with valsartan (Fig. 4). LCZ696 was also shown to have beneficial effects on renal function, with smaller mean decreases in estimated glomerular filtration rate from baseline compared with valsartan (−1.6 mL/min/1.73 m^2 versus −5.2 mL/min/1.73 m^2; $p = 0.007$) over 36 weeks [52]. LCZ696 had a favorable safety profile similar to that observed with valsartan.

An outcomes study (Prospective comparison of ARni with ARB Global Outcomes in heart failure with preserved ejectioN fraction [PARAGON-HF]) is currently planned to determine whether the promising biomarker results of LCZ696 in patients with HFpEF will translate into clinical benefit as measured by cardiovascular mortality and HF hospitalizations compared with valsartan.

Conclusion and future directions

The NP system has been shown to play an important cardiac and renal protective role. As a result it has been hypothesized that enhancing NPs may be beneficial in HF. Neprilysin inhibition enhances NP levels by reducing their enzymatic degradation. However, the utility of neprilysin inhibition requires management of the activation of the RAAS, which occurs with neprilysin inhibition alone. LCZ696, the first

ARNI in clinical development, meets this requirement since the compound enhances the actions of the NP system by inhibiting neprilysin while concurrently suppressing the activity of the RAAS by blocking the angiotensin AT_1 receptor.

Results from the clinical trial program of LCZ696 show that LCZ696 improves hemodynamics and cardiorenal biomarkers. Ongoing studies will determine whether these effects translate to improvements in outcomes of patients with chronic HF with either reduced or preserved LVEF. Additional studies of the NPs and of LCZ696 will be needed to further elucidate the mechanisms of its potential cardiorenal protection and the clinical relevance of the metabolic effects of the NPs.

Conflict of interest

Dr Langenickel is full time employee of Novartis Pharma AG, Basel, Switzerland, and Dr Dole is full-time employee of Novartis Institutes for Biomedical Research, Cambridge, MA, USA. Moreover, both authors are eligible to receive Novartis stock. The experimental and clinical studies of LCZ696 summarized in this review were supported and funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, Novartis Pharma AG, Basel, Switzerland and Novartis Institutes for Biomedical Research, Cambridge, MA.

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