The Path to an Angiotensin Receptor Antagonist-Neprilysin Inhibitor in the Treatment of Heart Failure

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ABSTRACT

The PARADIGM-HF (Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated that a new angiotensin receptor antagonist-neprilysin inhibitor was superior to an angiotensin-converting enzyme inhibitor in reducing mortality in patients with heart failure and reduced ejection fraction. This paper traces the research path that culminated in the development of this drug. The first phase, elucidation of the renin-angiotensin-aldosterone system, began with Tigerstedt’s discovery of renin, followed by isolation of angiotensin, isolation of angiotensin-converting enzyme, and synthesis of its inhibitors and of angiotensin receptor blockers. Phase 2 began with de Bold’s discovery of atrial natriuretic peptide, followed by isolation of the enzyme that degrades it (neprilysin) and its inhibitors. Phase 3 consists of blocking both the renin-angiotensin-aldosterone and atrial natriuretic peptide-degrading systems simultaneously. A molecular complex, LCZ696, developed by scientists at Novartis, combines an angiotensin receptor blocker with a neprilysin inhibitor, is well tolerated, and represents an important step in the management of heart failure and reduced ejection fraction. (J Am Coll Cardiol 2015;65:1029–41) © 2015 by the American College of Cardiology Foundation.

“If I have seen further, it is by standing on the shoulders of giants.”

—Isaac Newton, 1676

On March 31, 2014, the cardiology world, and many other medical professionals were excited by the press statement released by Novartis regarding a clinical trial on the treatment of heart failure (HF) with a new drug: “...the Data Monitoring Committee unanimously recommended early closure of the PARADIGM-HF [Prospective comparison of ARNi with ACEi to Determine Impact on Global Mortality and morbidity in HF trial], indicating patients with chronic heart failure with reduced ejection fraction [HFrEF] who received LCZ696 lived longer without being hospitalized for heart failure than those who received standard care with [angiotensin-converting enzyme] inhibitor [ACEI] enalapril. Based on the compelling efficacy and primary endpoint having been met, the trial will now close early” (2).

In the paper describing the design of the trial, McMurray et al. (3) outlined a comparison between LCZ696, a first-in-class angiotensin receptor-neprilysin inhibitor (ARNi), and enalapril. In another communication, the same authors stated that both components of the primary endpoint of the trial, cardiovascular death or hospitalization for HF, would “be analyzed separately and these additional analyses will be considered as part of the primary endpoint” (4). Therefore, there must have been compelling evidence that, when compared with enalapril in patients with HFrEF (5), LCZ696 further reduced not only the composite endpoint of cardiovascular death and hospitalization for HF, but also cardiovascular death alone.
The results of the PARADIGM-HF trial were presented at the European Society of Cardiology on August 30, 2014, and published simultaneously in the *New England Journal of Medicine* (6). It was praised in an accompanying editorial by Jessup, who wrote: “PARADIGM-HF may well represent a new threshold of hope for patients with heart failure...The beneficial results seen in PARADIGM-HF may apply to a wide spectrum of patients, even those who are currently receiving the best possible therapy” (7). A perspective in the same issue of the *New England Journal of Medicine* stated, “We may be entering a new era of treatment for heart failure with reduced ejection fraction” (8), strong words indeed by 2 editors of this journal.

LCZ696 is the first of a new class of drugs that simultaneously block the angiotensin II type I receptors (angiotensin receptor blocker [ARB]) and inhibit neprilysin (neprilysin inhibitor [NEPi]), hence, the acronym ARNI. This dual action places this drug at the center of 2 critically important systems that have profound effects on the circulation, as well as on other tissues: the renin-angiotensin-aldosterone system (RAAS), and the natriuretic peptide system (NPS) (Central Illustration). Although PARADIGM-HF appears to represent a very important advance in the treatment of HFrEF, LCZ696 did not burst on the scene like a comet from outer space, but instead represents the most recent in a series of brilliant investigations carried out over more than 11 decades. The objective of this paper is to summarize the key steps leading to this new therapy (Figure 1).

**RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM**

In 1898, Finnish physiologist Robert Tigerstedt, who can be considered to be the first giant on whose shoulders later investigators stood, and his Swedish medical student Per Bergman, working at the Karolinska Institute in Stockholm, discovered that when saline extracts of rabbit renal cortex were injected into rabbits, a pressor response was elicited (9,10) (Figure 2). They named the active component of the extract renin, which is now known to be an aspartyl protease. The next major step in the elucidation of the RAAS was taken in 1934, when Goldblatt et al. (11) demonstrated that constriction of the renal arteries of dogs caused persistent hypertension. Six years later, 2 groups, working in Argentina (12) and in the United States (13), demonstrated that renin catalyzed the formation of a peptide pressor substance, later named angiotensin. There were 2 forms of the latter, a largely inactive decapeptide (angiotensin I) that was cleaved by a second enzyme—a dipeptide hydrolase—angiotensin converting enzyme (ACE)—to form the active pressor substance, the octapeptide angiotensin II (Central Illustration). Subsequently, additional angiotensins, the products of further enzymatic hydrolysis, were discovered, but they are not central to this story (14).

In addition to its action on vascular smooth muscle, angiotensin II also causes retention of sodium by enhancing reabsorption of this ion in the proximal tubule and by stimulating the release of aldosterone from the zona glomerulosa of the adrenal cortex, thereby playing a critical role in the control of extracellular fluid volume and electrolyte balance. Angiotensin II also stimulates cell proliferation, oxidative stress, and fibrosis. The RAAS acts within the bloodstream, in a classical endocrine mode, and within the kidneys and other tissues in paracrine (local) and autocrine (intracellular) modes. ACE also inactivates the vasodilator peptide, bradykinin, which contributes to its pressor action, giving the enzyme its alternate name—kininase II.

**RAAS INHIBITORS.** As these important actions of ACE/kininase II became clarified, the search for inhibitors of this enzyme was begun. Ferreira made 2 important contributions. First, in 1965, he observed that the venom of *Bothrops Jararaca*, the Brazilian pit viper, contained an inhibitor of the kininase that degrades the vasodilator, bradykinin (15). Subsequently, he reported that this kininase inhibitor also inhibited ACE (16). He thus showed that the bradykinin potentiating substance and the ACEi were identical. The earliest ACEi/kininase were synthetic analogues of the active peptides in the venom and required parenteral administration. One of these, the nonapeptide, teprotide, was shown to reduce renal vasoconstriction, lower arterial pressure in hypertensive patients (17), and improve the disordered hemodynamics in patients with HF, demonstrating the important role of activation of the RAAS in the latter (18). Teprotide and other ACEis, in addition to raising bradykinin levels, increase the concentration of plasma and urinary prostaglandins, which are also vasodilators (19).

These favorable effects in patients with hypertension and with HF stimulated the development of orally active ACEis, the first of which was captopril, synthesized in 1977 by Ondetti et al. (20), a notable feat. Captopril soon became a useful antihypertensive (21). In animal studies, it prevented ventricular remodeling in rats with myocardial infarction (22) and reduced all-cause mortality when administered.
long-term to patients with left ventricular dysfunction following acute myocardial infarction (23). Other oral ACEis soon followed. Enalapril, the ACEi used as the comparator in the PARADIGM HF-trial (6), is a prodrug that is rapidly converted into enalaprilat, its active form. The latter was shown to prolong survival in severe HF (24), whereas the prodrug improved survival in chronic HFrEF (5). ACEis rapidly became, and remain, first-line drugs worldwide for the treatment of both hypertension and HF.

Although ACEis are well tolerated by the majority of patients, an annoying dry cough occurs in 10% to 15%. A related, but more serious adverse event, angioedema, can lead to life-threatening obstruction of the upper airway, and is caused by increased concentrations of bradykinin and vasoactive prostaglandins consequent to kininase inhibition. It occurs in 0.1% or 0.2% of Caucasians, but in a larger percentage of African Americans receiving ACEis.
After it was discovered that the actions of angiotensin II are mediated primarily by its type 1 receptor, a G-protein coupled receptor, the search for competitive blockers of this receptor (ARBs) began. Marshall et al. described the first of these, a peptide, in 1970. The angiotensin II analogue, saralasin, reduced arterial pressure in patients with malignant or resistant hypertension. Like the first ACEi, it was active only parenterally. Timmermans et al. described orally active nonpeptide ARBs with high affinity. Losartan was the first ARB to be used clinically; a closely related agent, valsartan, has been shown to improve outcomes in patients hospitalized for HF by Cohn et al. and is a component of the ARNi, LCZ696.

Like ACEIs, ARBs are potent antihypertensive agents and are indicated as first-line drugs in both hypertension and HFrEF. However, a major difference between ACEIs and ARBs is the greater specificity of the latter. Because ARBs do not block the degradation of kinins, angioedema and persistent cough are quite uncommon with their use. When blockade of the RAAS is desired, it is common clinical practice to begin with an ACEi and switch to an ARB in patients who are intolerant. Blockers of aldosterone and other mineralocorticoid receptors were described in 1959. By reducing renal sodium reabsorption, they have a diuretic action and have also been shown to reduce mortality in patients with HFrEF. These agents are also purported to exert antifibrotic actions.

**Natriuretic Peptide System**

In one of the first electron microscopic examinations of mammalian cardiac tissue, Kisch, in 1956, described granules in the atria. In 1978, Adolfo de Bold, another giant, and his collaborators, in Kingston, Ontario, suggested that these atrial granules were sites of storage of a protein or polypeptide. They then observed an inverse relation between water-electrolyte balance and atrial granularity, with hypergranularity developing in rats deprived of water and sodium, and the converse in sodium-loaded rats. In their now classic paper, published in 1981, they described an experiment that is reminiscent of the one reported by Tigerstedt and Bergman 83 years earlier. Their infusion of crude extracts of rat atrium caused hypotension and a more than 30-fold increase of sodium excretion, whereas urine volume rose 10-fold. de Bold et al. named the substance responsible for these effects.
atrial natriuretic factor, which has subsequently been referred to as atrial natriuretic peptide (ANP). They isolated and purified ANP, determined its amino acid sequence, and developed a radioimmunoassay (35), establishing the heart to be an endocrine organ (36). An endocrine function of the heart had, in fact, been suggested in 1964 (37).

In 1988, Sudoh et al. (38), in the first of several important contributions to this field, identified a peptide in porcine brain and named it brain natriuretic peptide (also known as B-type natriuretic peptide [BNP]). Although not identical to ANP, BNP has similar structural, hypotensive, natriuretic, and diuretic properties. BNP is also present in the heart and is released primarily from the ventricles (39). A third peptide in this family, C-type natriuretic peptide (CNP), was also extracted first from porcine brain, and then from endothelial cells (40).

These 3 peptides, which form the natriuretic peptide system (NPS), are the products of separate genes that encode 3 prohormones. The latter undergo proteolytic cleavage to form the 3 active hormones having several structural homologies. ANP has 28, BNP has 32, and CNP has 22 amino acids. ANP and BNP bind to and activate membrane-bound natriuretic peptide receptors-A (Central Illustration). These are coupled to and activate guanylyl cyclase A, which increases the intracellular concentrations of the second messenger, cyclic guanosine monophosphate (41). The latter, in turn, activates protein kinase G, leading to vasorelaxation, natriuresis, and diuresis (42). ANP and BNP also inhibit renin secretion (43) and aldosterone production (44) and attenuate cardiac and vascular remodeling, apoptosis, ventricular hypertrophy, and fibrosis (44–47); they also enhance myocardial relaxation. CNP is released primarily from endothelial cells, and only trace quantities are found in the blood. In contrast to ANP and BNP, CNP appears not to exert a marked effect on sodium or water excretion, but instead to act as a vasodilator in paracrine and autocrine modes and to stimulate the growth of long bones (41,45,48). Although it may seem inappropriate to label CNP as a “natriuretic” peptide (NP), all 3 polypeptide hormones are still widely referred to as NPs, and constitute the NPS.

Distension of the atria and ventricles, as occurs in cardiac injury and/or overload, ventricular dysfunction, and HF results in significant increases in the expression of ANP and BNP. In 1986, Burnett (49), another important investigator in this field, and his collaborators demonstrated elevations of circulating ANP in patients with HF. The concentrations of circulating BNP and of its inactive precursor, N-terminal fragment of pro-B-type natriuretic
peptide (NT-proBNP) have become extremely valuable in the recognition of hemodynamic overload, ventricular dysfunction, and HF (50,51). Measurements of these peptides are also useful in assessing prognosis and monitoring therapy, and appear to be useful as therapeutic targets as well (52). Although the infusion of synthetic human ANP, named carperitide (53), and human recombinant BNP (nesiritide) have exhibited the desired physiologic effects (i.e., vasorelaxation, natriuresis, and diuresis) and have been approved for the treatment of HF in some countries, they require parenteral administration and have yet to demonstrate an unambiguous improvement in clinical outcomes (54).

ADRENOMEDULLIN. In 1993, Kitamura et al. (55) isolated another novel, potent, hypotensive peptide composed of 52 amino acids from human pheochromocytoma, as well as from normal adrenal medulla, which they termed adrenomedullin (ADM). Although it shares the vasorelaxant and natriuretic properties of ANP and BNP, ADM is structurally unrelated. ADM has also been shown to reduce myocyte hypertrophy, fibroblast proliferation, collagen synthesis, and aldosterone secretion. Kitamura developed a sensitive radioimmunoassay for ADM, reported its presence in normal human plasma (55), and characterized the complementary deoxyribonucleic acid encoding the precursor of the peptide. The vascular endothelium is now also known to produce ADM, and it is found in many organs, including the kidney, where it reduces renal vascular resistance and increases glomerular filtration rate (56).

Infusion of ADM into normal subjects showed it to be a potent vasodilator. In patients with HF, it reduces systemic and pulmonary arterial and wedge pressures and plasma aldosterone, while raising cardiac output, urinary volume, and sodium excretion (57). ADM acts on a specific receptor, 1 of the so-called calcitonin gene-related peptide receptors, elevates intracellular cyclic adenosine monophosphate, and increases intracellular [Ca2+]i, which, in turn, activates NO synthase and intracellular NO; the latter is believed to be responsible for the vasodilator action of ADM (56).

In 1995, Jougasaki et al. (58) reported elevations of circulating ADM in patients with HF, and plasma ADM was found to be an independent predictor of prognosis in such patients. However, the clinical applicability of ADM measurements has been limited by the instability of the molecule. An assay for the midregion of pro-adrenomedullin to be superior to NT-proBNP for the prediction of mortality in patients with acute HF (60). Given the salutary properties of ADM, it would seem that enhancement of circulating ADM could be beneficial in patients with HF.

NEPRILYSIN AND ITS INHIBITION

Circulating NPs are cleared through 2 principal mechanisms: NP receptor-mediated clearance and enzyme degradation (61,62). An important paper published in 1974 by Kerr and Kenny (63) described a neutral glycosylated zinc endopeptidase in the proximal tubule cells of the rabbit kidney. An equally important study by Stephenson and Kenny showed it to be a potent hydrolyzer of ANP (64). The production and release of this enzyme from endothelial cells contributes to its presence in the circulation (65). The abundance of this peptidase in the renal cortex contributes to the very brief half-life of ANP (approximately 2 min in normal human subjects) (66). Although attention was initially directed to its ability to hydrolyze ANP (63), this membrane-bound enzyme with a large extracellular component also degrades a large number of other vasodilator peptides, including ADM (67), and bradykinin, vasoconstrictors including angiotensins I and II and endothelin-1, as well as oxytocin, opioid peptides, substance P, gastrin, vasoactive intestinal peptide, and amyloid beta protein (68). However, BNP is relatively resistant to its digestion. Given this enzyme’s broad action profile, it has had a variety of names, including atriopeptidase, neutral endopeptidase, EC 3.4.24.11, enkephalinase, common acute lymphoblastic leukemia antigen, CD10, as well as nephrilysin (NEP) (61); the latter will be the designation used in this paper (Figure 1).

NEP INHIBITION. In 1980, Roques et al. (69) synthesized thioran, a NEPi. Sybertz et al. (70) then showed that by inhibiting NEP, endogenous ANP levels rose, and the latter’s natriuretic and diuretic properties became evident. Similar observations were made in normal humans (71). In 1995, Ksander et al. (72) at Ciba-Geigy (which became an important unit of Novartis) described sacubitril, a NEPi that had superior pharmacologic properties, and which later became a component of LCZ696. NEPi caused diuresis in pacing-induced HF in sheep (73) and dogs (74), and suppressed the activation of aldosterone (75), demonstrating the important interaction between the NPS and RAAS. In patients with HF, NEPi lowered both right atrial and wedge pressures and caused natriuresis (76).
It was hoped that NEPis would become useful in the management of hypertension and HF, but these beneficial effects in patients were modest and were not seen in all studies (77). In addition to increasing the concentration of circulating ANP (78), NEPis were found to increase the concentration of 2 other circulating vasodilators, ADM and bradykinin (78,79). However, they also increased the concentration of 2 circulating pressors, angiotensin II and endothelin I (80,81). These 2 opposing actions, that is, inhibition of degradation of both vasoconstrictor and vasodilator peptides, neutralized each other and, as a consequence, NEPis alone had little effect on blood pressure (82) or HF (77).

With the discovery and elucidation of the actions of NEP and its inhibitors, both the similarities and differences between the RAAS and the NPS became clearer (Central Illustration). In normal subjects, the RAAS is activated, in part, by reduced stretch of the efferent renal arterioles as well as by stimulation of beta-1-adrenergic receptors through activation of the sympathetic nervous system. Activation of the sympathetic nervous system and RAAS provides an adaptive response to hypovolemia, hypotension, and sodium deprivation. This response includes the release of renin, mostly from granular juxtaglomerular cells in the walls of the afferent arterioles of the kidney, leading to the production of the pressor angiotensin II. This, in turn, causes vasoconstriction of renal efferent arterioles, as well as release of aldosterone, increasing sodium reabsorption in the collecting duct. However, because these actions are maladaptive when they occur in patients with HF or hypertension, reducing the generation of angiotensin II by ACEi or blocking its action with an ARB are beneficial in these conditions. In contrast, atrial and/or ventricular distension, as occurs in HF and hypertension, causes the release of NPs from the heart, which results in vasodilation and natriuresis. Although these actions are beneficial (adaptive) in patients with HF or hypertension, rapid enzymatic degradation of ANP by endogenous NEP greatly diminishes their vasorelaxant, natriuretic, and diuretic actions. NEPis, while raising the concentration of circulating vasodilator peptides, especially ANP, have complex actions (as outlined earlier) and appear by themselves not to be useful in the treatment of either HF or hypertension.

**VASOPEPTIDASE INHIBITION**

Because the previously mentioned elevation of circulating angiotensin II by NEP (80,81) neutralizes its salutary vasorelaxant and natriuretic actions, it appeared logical to ascertain whether the suppression of angiotensin II production would correct this problem. In an important study published in 1991, Seymour et al. (83) compared the separate administrations of a selective NEP inhibitor and of the ACEi captopril, as well as their simultaneous administration, into hypertensive rats. As predicted, the combination resulted in a greater reduction of arterial pressure than each inhibitor given separately (83). These observations on the greater efficacy of dual therapy were confirmed in cardiomyopathic hamsters (84), as well as in dogs and sheep with pacing-induced HF (85,86). The next important step was to develop orally active molecules that inhibited both ACE and NEP, that is, dual inhibitors. This was accomplished by Fournie-Zaluski et al. in 1994 (87).

Because of the potential promise of oral dual inhibitors, referred to as vasopeptidase inhibitors, several pharmaceutical companies entered the field. Omapatrilat was the drug in this class that underwent the most extensive clinical testing (88). It produced greater reductions in arterial pressure than did the ACEi, lisinopril, in patients with hypertension and increased the excretion of ANP, confirming that the dose used also exerted significant inhibition of NEP (89). IMPRESS (Inhibition of Metalloprotease by Omapatrilat in a Randomized Exercise and Symptoms Study in Heart Failure), a randomized clinical trial, compared omapatrilat with lisinopril in 573 patients with HFrEF (90); a strong trend toward greater benefit with omapatrilat was reported. These early clinical studies generated considerable excitement; indeed, in 2001, it was anticipated that omapatrilat would be launched in 2002 or early 2003, and that annual sales would quickly approach $2 billion (91).

A phase 3 trial in HF, the OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) trial led by Packer, compared omapatrilat with enalapril in 5,770 patients with HF. There was a nonsignificant trend for superiority of omapatrilat in the primary endpoint (all-cause mortality or hospitalization for HF) and a significant reduction of the secondary endpoint of cardiovascular death or hospitalization (92). However, angioedema, which can obstruct the upper airways, occurred more frequently with omapatrilat (0.8%) than with enalapril (0.5%). In 4,284 hypertensive subjects in phase 3 trials of omapatrilat, 0.9% developed angioedema and an additional 1% developed “head and neck edema” (93). In order to obtain a clearer understanding of the frequency of this complication, and, in particular, to compare omapatrilat with an ACEi, lisinopril, the OCTAVE...
(Omapatrilat Cardiovascular Treatment vs. Enalapril) trial was conducted in 25,302 hypertensive subjects. As expected, omapatrilat was superior to lisinopril in reducing blood pressure. However, the incidence of angioedema was again significantly higher and more severe in the subjects treated with omapatrilat (2.17%) than in those receiving lisinopril (0.68%). Among African American patients, the incidence was greater for both agents (5.53% vs. 1.62%) (93). The increased incidence of this serious, potentially life-threatening complication was presumed to be related to the synergism between the ACE- and NEP-inhibiting actions of omapatrilat on the degradation of bradykinin (94). Omapatrilat inhibits a third enzyme, aminopeptidase P, which is also involved in the breakdown of bradykinin (95). Bradykinin is not only a vasodilator, but it also enhances prostaglandin concentrations (19) and increases vascular permeability and fluid extravasation. Hence, the question was raised as to whether omapatrilat, which initially appeared to be an attractive drug, could be a “double-edged sword” (96). Primarily on the basis of observations of increased angioedema in the OCTAVE trial, efforts to gain approval of omapatrilat approval and, indeed, further clinical research on the entire class of vasopeptidase inhibitors were halted.

The next step was to combine the efficacy of vaso-peptidase inhibitors, that is, suppression of the RAAS and inhibition of NEP, without their principal adverse effect, that is, the inhibition of bradykinin and the resultant angioedema. This was accomplished simply and cleverly by replacing the ACEi in omapatrilat with an ARB, because (in contrast to ACEIs), ARBs do not inhibit the breakdown of bradykinin, with a resultant reduction of the risk of angioedema. In 2003, the Novartis Pharmaceutical Corporation applied for the patent of a drug comprising a combination of the angiotensin antagonist valsartan and an NEPi, naming Webb and Ksander as the inventors (97). LCZ696 is a supramolecular complex of 6 molecules of the ARB valsartan with 6 molecules of the NEPi pro-drug, sacubitril (AHU377), creating a novel crystalline complex having a molecular weight of 5,748 (98) and a first-in-class ARNi. Following ingestion, sacubitril is metabolized rapidly into the active NEPi, LBQ657. Gu et al. (95) published phase I and II studies on LCZ696 in 2010; the peak concentrations of both valsartan and LBQ657 occurred at about 3 h following oral administration. The action of the ARB was reflected in the rapid increases in the plasma renin and angiotensin II concentrations. Simultaneously, cyclic guanosine monophosphate rose, reflecting an increase in the concentration of ANP resulting from the NEPi action of LBQ657.

In 2010, Ruilope et al. (99) compared LCZ696 with valsartan in 1,328 hypertensive subjects. Systolic, diastolic, and pulse pressures, both sitting and ambulatory, fell to a greater extent with LCZ696 than with either valsartan or the NEPi prodrug (AHU377) administered separately (Figure 3) (99). LCZ696 was well tolerated, without excess cough and with no instances of angioedema. Similar findings were reported in an Asian population of hypertensive subjects (100). Solomon et al. (101) conducted the PARAMOUNT (Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejectionfracTion) trial, a double-blind randomized trial in 301 patients with heart failure with preserved ejection fraction (HfPEF), which compared LCZ696 with valsartan. The primary endpoint, the decline in NT-proBNP at 12 weeks after treatment was begun, was significantly greater in the LCZ696 group than in the valsartan group (Figure 4). After 36 weeks, both left atrial volume and dimension, which reflect left ventricular filling pressure, also declined more with LCZ696 (Figure 4), and there was greater improvement in the New York Heart...
Association functional class with LCZ696 than with valsartan.

In the PARADIGM-HF trial led by McMurray, Packer, and other academic investigators collaborating with scientists at Novartis, LCZ696 was compared to the ACEi enalapril in 8,442 symptomatic patients with HFrEF. As already noted, the trial was stopped early for clinical benefit after a median follow-up of 27 months (2,6). The hazard ratio for the primary endpoint (cardiovascular death or hospitalization for HF), was 0.80; this ratio was also 0.80 for cardiovascular death, was 0.79 for hospitalization for HF, and was 0.84 for death from any cause. The reductions in hazard ratios in each of these important endpoints were highly significant (p < 0.0001). Over the course of the trial, the number of patients who needed to be treated to prevent 1 primary endpoint was 21, and to prevent 1 cardiovascular death was 32. Although LCZ696 was associated with symptomatic hypotension more frequently than was enalapril, this did not lead to more drug discontinuation. Elevations of serum creatinine (≥2.5 mg/dl), potassium (≥6 mmol/l), and cough occurred significantly less frequently with LCZ696 than with enalapril. However, there was a nonsignificant trend for an increase in angioedema (without airway compromise) with LCZ696 (n = 19) compared with enalapril (n = 10; p = 0.13).

In a more recent report, the PARADIGM investigators (102) indicated that, in comparison with enalapril, LCZ696 exhibited additional evidence of clinical benefit, including a reduced need for intensification of the treatment for HF, fewer visits to an emergency department for HF, and a lower requirement for intensive care or need for inotropic agents, an HF device, or cardiac transplantation. Progressive symptoms of HF and elevations of NT-proBNP and troponin were also reduced.

Although the results of PARADIGM HF are remarkably robust and promising, after the drug has been approved, post-marketing observations will be of interest. Patients in the trial had a run-in period and were randomized only if they tolerated both study drugs. Both hypotension and a numeric increase of angioedema with LCZ696 were observed in PARADIGM HF, but neither led to serious consequences. It will be important to ascertain how the drug is tolerated when it is used in clinical practice.

THE FUTURE

**HF WITH PRESERVED EJECTION FRACTION.** The PARAMOUNT study (101) served as a hypothesis-generating trial for HFP EF. Given PARAMOUNT’s encouraging results (Figure 4), the PARAGON (Prospective Comparison of LCZ696 with ARB Global Outcome in HF with Preserved Ejection Fraction) trial (NCT01920711) has begun. It is intended to enroll 4,300 patients with left ventricular ejection fraction >45%.

**RENAL DISEASE.** There is now good evidence that blockade of the RAAS by either ACEi or ARB slows progression in patients with chronic kidney disease, with and without diabetes (103,104). The NEPi, candesartan, has been shown to be associated with natriuresis in patients with moderate impairment of renal function (105). Studies in partially nephrectomized rats (106) and in rats with diabetic nephropathy (107) have demonstrated that the vasopeptidase inhibitor, omapatrilat, was superior to an ACEi in slowing the progression of renal injury in the remaining renal tissue. In both the IMPRESS (90) and OVERTURE (92) trials, omapatrilat was associated with significantly fewer instances of worsening renal function than the ACEi comparator. Similar findings were observed with LCZ696 in the PARAMOUNT trial (101). Also, in the PARADIGM-HF trial, which excluded patients with an estimated glomerular filtration rate <30 ml/min, fewer patients on LCZ696 developed a serum creatinine level ≥2.5 mg/dl (n = 139, 3.3%) than did patients on enalapril (n = 188, 4.5%; p = 0.007) (6).
The totality of this information suggests that LCZ696 may be superior to blockers of the RAAS on renal function. This is being tested prospectively in the UKHARP (UK Heart and Renal Protection) III trial (ISRCTN11958993), which is comparing LCZ696 with the ARB, irbesartan, in patients with proteinuric renal disease and an estimated glomerular filtration rate $\geq 20$ and $< 60 \text{ ml/min/1.73 m}^3$ (108). Furthermore, because HF is a common, serious complication in patients with end-stage renal disease, LCZ696 might retard the development and/or progression of both conditions.

**AORTIC STIFFNESS.** In the elderly, the stiffness of the aorta and large arteries raises the systolic blood pressure, pulse pressure, and pulse wave velocity, all of which are independent predictors of adverse cardiac events (109,110) and of the progression of renal disease (111). It has been shown that noninvasively determined central aortic blood pressure is superior to brachial arterial pressures in estimating cardiovascular risk (112). In the Strong Heart study, central (aortic root) systolic pressure was a potent predictor of left ventricular hypertrophy, whereas pulse pressure was a predictor of vascular hypertrophy (113). In 2002, Mitchell et al. (114) demonstrated the superiority of omapatrilat over enalapril in reducing both central aortic and peripheral arterial pulse pressures, reflecting a reduced stiffness of the aorta, perhaps brought about by the elevation of circulating ANP consequent to the NEPl activity of omapatrilat.

In the aforementioned study of hypertensive subjects, LCZ696 reduced both ambulatory systolic and pulse pressures more than did valsartan (99), a finding that is compatible with a reduction of aortic stiffness. Accordingly, the PARAMETER (Prospective comparison of Angiotensin Receptor neprilysin inhibitor with Angiotensin receptor blocker Measuring arterial stiffness in the Elderly) study (NCT01692301) is comparing LCZ696 with an ARB (olmesartan) in 432 elderly (age $\geq$60 years) hypertensive patients with a pulse pressure $>60$ mm Hg (109). The endpoints are changes in central aortic systolic and pulse pressures determined noninvasively (115). LCZ696 is also promising for the treatment of serious and/or resistant hypertension.

**CONCLUSIONS**

The unambiguous superiority of clinical outcomes in patients with HFrEF by the first ARNi over enalapril in the PARADIGM HF trial (6,102,116) represents a significant achievement with important clinical implications. LCZ696 may replace conventional ACEis or ARBs in many patients with chronic HFrEF. The potential value of LCZ696 in HFpEF; in acute HF; in HF patients with the cardiorenal syndrome; in the prevention of HF in asymptomatic patients with left ventricular hypertrophy, dilation, and/or dysfunction; and in severe hypertension remains to be determined.

LCZ696 developed from the stepwise research described herein (Figure 1). Progress was slow in the first half of the 20th century, but it then accelerated progressively, especially after de Bold’s important discovery in 1981 (34). Academic scientists carried out the initial work defining the components of both the RAAS and the NPS, some of whom conducted early experiments on blocking these systems. Once it was realized that blockade was potentially of great clinical value, the pharmaceutical industry stepped in and provided enormous talent and resources to move the field forward. Millions of patients with hypertension and HF worldwide have benefited from ACEis and ARBs, which are among the most useful drugs in the pharmacopeia. The most recent advance, the development and clinical assessment of a drug that simultaneously blocks the RAAS, inhibits the breakdown of vasodilator peptides, and appears to be well tolerated, is an excellent example of the synergies that can result from academic-industrial collaborations.

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