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Lessons from the trials

PARADIGM-HF: Have we achieved a new paradigm in the treatment of heart failure?

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PARADIGM-HF

After several years of a disappointing series of negative clinical trials investigating novel therapies for systolic heart failure, the presentation of the landmark PARADIGM-HF [Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure] trial at the 2014 Congress of the European Society of Cardiology in Barcelona, with simultaneous publication in the *New England Journal of Medicine*,[1] has created considerable excitement and optimism. With knowledge that the trial had been halted prematurely by the independent data and safety monitoring committee (DSMB), the results were eagerly anticipated, and the trial results lived up to the expectations.

PARADIGM-HF investigated the impact of LCZ696 (the novel combination of an angiotensin-receptor blocker (ARB) plus the neprilysin inhibitor sacubitril) compared to the angiotensin converting enzyme (ACE) inhibitor enalapril on outcomes of 8442 patients with heart failure and left ventricular systolic dysfunction (ejection fraction 40%). ACE inhibitors have been the cornerstone of treatment for heart failure with reduced ejection fraction for over two decades and are firmly embedded in U.S. and European guidelines for the management of heart failure.[2,3] Virtually all patients in the trial were receiving ACE inhibitors or ARBs prior to enrollment but had persistent left ventricular dysfunction. The trial randomly assigned 4187 patients to receive LCZ696 200 mg twice daily and 4212 to receive enalapril 10 mg twice daily. The 200 mg dose of LCZ696 includes the ARB equivalent of 160 mg of valsartan. Background therapy included beta adrenergic receptor blockers in 93% of patients and mineralocorticoid antagonists in 56%. The primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was also designed as a cardiovascular mortality trial with the power to detect a 15% reduction in mortality with LCZ696 compared to enalapril, which would represent a doubling of survival benefit relative to that of current inhibitors of the renin-angiotensin system. The DSMB was allowed to halt the trial prematurely only if there was a compelling effect on cardiovascular mortality.

The DSMB stopped the trial after a median follow-up period of 27 months, because of evidence of significant benefit of LCZ696, with cardiovascular mortality rates of 13.3% in the LCZ696 group and 16.5% in the enalapril group (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.71 to 0.89; $P < 0.001$). At the time of trial termination, 21.8% of the LCZ696 group and 26.5% of the enalapril group had reached the primary combined endpoint (HR 0.80; 95% CI, 0.73 to 0.87; $P < 0.001$). LCZ696 was also associated with lower overall mortality 17.0% versus 19.8%; HR 0.84; 95% CI, 0.76 to 0.93; $P < 0.001$), reduced risk of hospitalization (21% decrease, $P < 0.001$) and reduced symptomatic limitation ($P = 0.001$). Hypotension and non-serious angioedema occurred more frequently in the LCZ696 group, but renal impairment, hyperkalemia, and cough occurred more frequently in the enalapril group.

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The magnitude of effect of LCZ696 in reducing cardiovascular mortality is twice that achieved by ACE inhibitors alone in the seminal trials of ACE inhibition[4,5] and more than twice that achieved in trials of ARBs.[6] This incremental survival benefit in patients also receiving evidence-based use of beta-blockers and mineralocorticoid antagonists indicates that combined angiotensin receptor-neprilysin inhibition (ARNI) has the potential to be transformative in the management of patients with systolic heart failure.

NEPRILYSIN INHIBITION

Neprilysin is a neutral endopeptidase that degrades natriuretic peptides, bradykinin, adrenomedullin, and other endogenous vasoactive peptides[7] with the resulting neurohormonal effects of sodium retention, vasoconstriction, and myocardial hypertrophy and fibrosis (Figure 1).

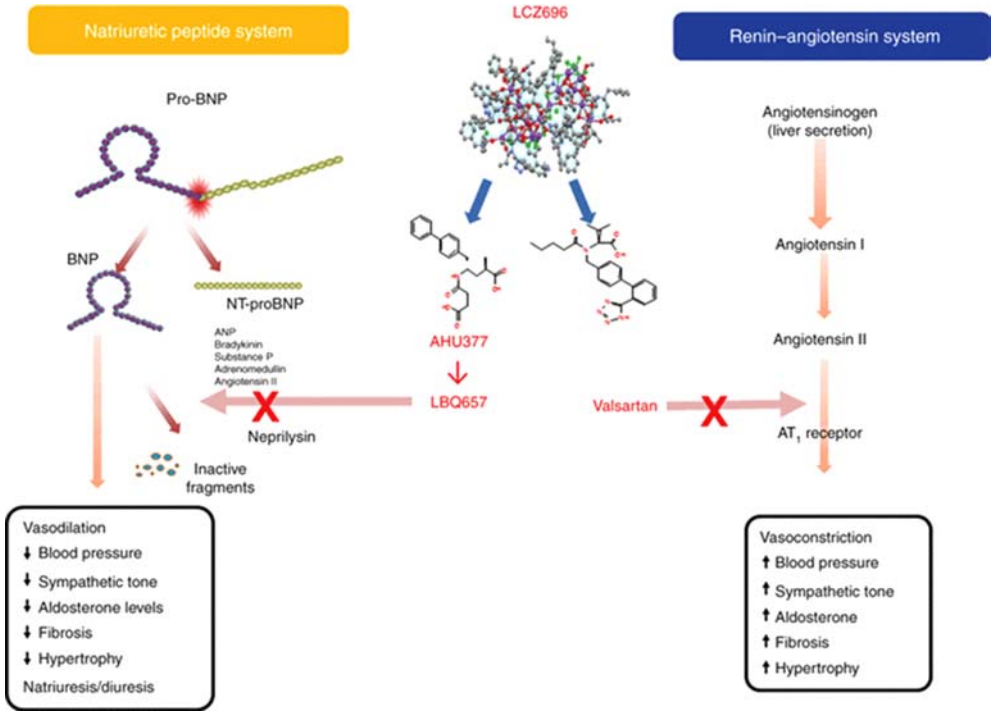

Figure 1. Mechanism of action of LCZ696. LCZ696 is a dual-acting neprilysin inhibitor and angiotensin receptor blocker as it comprises the molecular moieties of both sacubitril (AHU337) and valsartan. AHU377 is converted to the active neprilysin inhibitor LBQ657, which inhibits the neprilysin enzyme, responsible for the breakdown of the biologically active natriuretic peptides, including BNP, ANP, bradykinin, substance P, adrenomedullin, and angiotensin II. BNP contributes to natriuresis, diuresis, and vasodilation. The biologically inert NT-proBNP is not a substrate of this enzyme and is therefore unaffected by its inhibition. The valsartan component blocks the angiotensin II receptor type 1 (AT1) receptor, thus negating the effects of angiotensin II. The net combined effect is inhibition of neprilysin and the renin-angiotensin system. ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide. *Reproduced with permission from Vardeny et al.*[8]

Neprilysin inhibition is thus an attractive target in treating symptomatic heart failure, and early experimental studies indicated that combined inhibition of the renin-angiotensin system and neprilysin was superior to targeting either pathway alone. However, clinical trials with omipatrilat, a dual inhibitor of both ACE and neprilysin, was not more effective than enalapril alone in reducing a combined endpoint of mortality and hospitalization[9] and was associated with significant adverse effects including hypotension and serious angioedema.[9,10] Angioedema was particularly problematic in African American patients. LCZ696 was designed with an ARB instead of ACE inhibitor to minimize the possibility of angioedema.

In PARADIGM-HF, a run-in phase was conducted prior to randomization in which potential patients entered a run-in period of enalapril pretreatment (medial duration 15 days) followed by a run-in period of LCZ696 pretreatment (median 29 days) to assess safety and tolerability.[1] It is noteworthy that 10,513 patients were enrolled, but 2079 patients (20%) dropped out during the pretreatment run-in phases of

the trial, resulting in the 8442 who underwent randomization. The predominant reasons for drop out were significant adverse drug effects and development of abnormal laboratory values.

WILL PARADIGM CHANGE THE TREATMENT PARADIGM?

The implications of ARNI treatment in this trial are very significant, in terms of survival and quality of life, and could lead to approval of this drug combination in many countries. However, several ongoing issues remain that will need further exploration before this novel therapy should be considered for all patients. Most noteworthy, as indicated above, is the careful design of the trial to exclude patients who would not tolerate ACE inhibition or ARNI, which excluded 20% of potential candidates for therapy despite that fact that virtually all were taking an ACE inhibitor or ARB before enrollment. Lack of tolerability in one-fifth of patients indicates the need to better identify those most likely to receive ARNI safely. The patients in the trial were predominantly Caucasian (66%) and from Europe (58%), with only 18% from Asia and 7% from North America. Whether similar benefits and safety will be achieved in more diverse populations (including African Americans) and in different regions such as Asia, the Middle East, and the Americas are yet to be determined. Only 15% of patients had implantable defibrillators despite the indication for device therapy in the majority of patients, and only 7% received biventricular pacing for cardiac resynchronization. Whether the survival benefit with ARNI therapy is greater than that which might be achieved with device therapy is unclear, although the improvement in symptoms with ARNI cannot be discounted. Finally, and perhaps most importantly, only 24% patients enrolled in PARADIGM-HF were in New York Heart Association (NYHA) functional class III and less than 1% were in functional class IV. The point estimates for the primary combined endpoint were less convincing in the subgroup of patients in NYHA functional class III-IV. Thus, this should be considered a trial of mild to moderate heart failure, not severe symptomatic heart failure. ARNI therapy should be used advisably in patients with severe heart failure symptoms until more outcome and safety data emerge in such patients.

WHAT HAVE WE LEARNED?

PARADIGM-HF represents a major step forward in the treatment of patients with heart failure, with the cautionary notes indicated above. Considering the growing global burden of heart failure, the results of this trial provide a note of optimism that progress is being made. ARNI therapy has the potential to improve outcomes in many patients who remain symptomatic and at risk despite current evidence-based therapies, although more work needs to be done. This new treatment option from this landmark trial will undoubtedly inform future guidelines deliberations.

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