Editorial

Prospective Comparison of ARNi With ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF)

Paragon of a Study or Further Investigation Paramount?

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The Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study clearly represents a landmark in the history of heart failure (HF) trials. Not since the era of β-blocker HF studies have we had a new class of agent for this condition that not only met its primary efficacy end point but also resulted in a stand-alone mortality benefit compared with conventional therapy, and did so with an acceptable safety profile. What was missing from the PARADIGM-HF main results article, however, was the clinical impact of the novel intervention, an angiotensin receptor neprilysin (or neutral endopeptidase) inhibitor (ARNi), over the period of follow-up postrandomization. That gap in our knowledge regarding clinical outcomes of this new agent has now been addressed by the article by Packer et al2 in this issue of Circulation. These new findings are focused entirely on surviving patients, drilling down into their clinical course, resource use, and in particular hospitalization requirements. From the data presented, a clear picture emerges of fewer hospitalizations and less need to intensify therapy (via increased use of pharmacological agents, implantation of devices, or cardiac transplantation) with the ARNi, LCZ-696, in comparison with the angiotensin converting enzyme (ACE) inhibitor, enalapril. In addition to clear data supporting attenuated worsening of clinical status, there was also strong evidence that patients had improved quality of life (as assessed by Kansas City Quality of Life Questionnaire) and overall clinical status (as assessed by New York Heart Association functional class) with LCZ-696 versus enalapril. These clinical findings were also supported by favorable biomarker data.

These data are all the more impressive given that more patients died in the enalapril group than the LCZ-696 group over the course of the PARADIGM-HF study.1 Thus, the pool of surviving patients was larger within the LCZ-696 group and a greater number potentially able to be hospitalized. As well, more of the sicker patients had been “removed” from the enalapril group via premature death. The above issue of “competing risks” is highly relevant to the interpretation of these clinical data in surviving patients. Not only were first hospitalizations reduced but also recurrent hospitalizations. This latter end point is of course highly relevant to not only the patient and treating physician, but also to healthcare payers. For this reason, recurrent HF hospitalisation is increasingly being used in clinical trials for regulatory purposes as a formal end point, rather than just a post hoc analysis.

The clinical efficacy benefits of LCZ-696 do, however, have to be weighed against the side-effect profile of the new drug. This specific article does not focus in on adverse events, however the side-effect profile of LCZ-696 was characterized fairly comprehensively in the main results article.1 Symptomatic postural hypotension was greater in the LCZ-696 group compared with enalapril and may limit clinical utility, particularly in those with borderline blood pressure levels before commencement of therapy. Undoubtedly, an analysis of the utility of this agent according to baseline blood pressure will be forthcoming in future studies. It has to be remembered that this increase in hypotension occurred despite a very carefully controlled run-in period whereby patients were exposed to both ACE inhibitor and LCZ-696, sequentially. Patients not tolerating this run-in for hypotension (or other reasons) were removed from the trial before randomization. Therefore, in the real world it may be expected that this adverse event will occur with even greater frequency and certainly needs to be carefully followed in postmarketing surveillance if/when the drug is approved. The other major adverse event of concern is the nearly double rate of angioedema with LCZ-696 versus enalapril. Angioedema was first observed with the ACE/neprilysin inhibitor, omapatrilat.3 Although not a major issue within the omapatrilat HF program, life-threatening angioedema did occur in hypertensive patients, particularly those of African-American ethnicity.4 Omapatrilat inhibits not only ACE and neprilysin but also aminopeptidase-P5, all potentially capable of bradykinin augmentation. It was anticipated that combining an angiotensin receptor blocker with neprilysin inhibition would alleviate this issue, but in fact more cases were observed with LCZ-696 than enalapril (19 in LCZ-696, 10 in enalapril patients) in PARADIGM-HF. Bradykinin levels have previously been shown to increase with angiotensin receptor blocker therapy,6 and thus the angioedema risk may not be nonexistent nor even trivial. This also needs further careful assessment in weighing up risks and benefits of this new therapy. In addition, amyloid β is also a substrate for neprilysin,7 and inhibition may block breakdown of this key peptide implicated in Alzheimer disease pathogenesis and progression.
It is to be hoped that ongoing and future studies such as the PARAGON-HF (Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction) study in patients with HF and preserved ejection fraction (which follows on from favorable surrogate data obtained from PARAMOUNT [Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction], in a similar patient population) will assess this (thus far) theoretical concern, via evaluations such as cognitive function testing. Having said that, this may be an issue more relevant to disease states with greater longevity than HF.

A further issue regarding these new clinical data regarding LCZ-696 is what mechanistic insight they might provide as to why this drug was superior to conventional therapy with ACE inhibitor. An indirect clue regarding mechanism of benefit is provided by the accompanying biomarker data, in particular, evidence for on-target effects of ARNi, supported by the expected elevation of plasma brain natriuretic peptide levels as well as increase in urinary cyclic guanosine monophosphate levels (guanosine monophosphate mediates many of the putative beneficial effects of the natriuretic peptides). Evidence that this may translate into reduced myocardial wall stress or ischemia is supported by reduced N-terminal pro–brain natriuretic peptide levels (which should be unaffected directly by nephrilysin inhibition) and lower serum troponin levels. However, it remains uncertain whether this is a direct effect on the heart or indirect secondary to the beneficial effects of this agent on the vasculature (where lower systemic blood pressure levels may be a surrogate for such efficacy) or on the kidney, where deterioration in renal function consistently occurs with less frequency than with conventional therapies,

It should be emphasized that PARADIGM-HF was not a mechanistic study and cannot directly answer these questions. This is especially so because it cannot be said with certainty that the magnitude of achieved renin-angiotensin-aldosterone blockade was the same across the 2 therapies (valsartan moiety of LCZ-696 versus enalapril). PARADIGM-HF should rather be viewed as a pragmatic study asking the question of whether the newer agent is clinically superior to current best practice management of systolic chronic HF patients. By any measure, in both the main article and the new data published in this issue of Circulation, the ARNI LCZ-696 clearly meets any and all reasonable criteria for clinical superiority versus conventional therapy.

**Disclosures**

Dr Krum has received research contracts and served as a consultant to Novartis.

**References**


**Key Words:** Editorials ■ angiotensin receptor blocker ■ heart failure ■ natriuretic peptide
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