EDITORIALS

Neprilysin Inhibition — A Novel Therapy for Heart Failure

Mariell Jessup, M.D.

The Food and Drug Administration (FDA) last approved a new oral drug (hydralazine–isosorbide dinitrate) for patients with heart failure and a reduced ejection fraction in 2005 — and this drug was recommended only for self-identified black patients who continued to have symptoms despite evidence-based treatment.[1] The aldosterone antagonist eplerenone was approved for the treatment of heart failure in 2003. (In 2012, the European Medicines Agency approved ivabradine, which has not received FDA approval.) Now, a novel drug, LCZ696, a dual inhibitor of angiotensin II receptor and neprilysin, may prove to be the first disruptive agent to the heart-failure treatment algorithm, which has remained essentially unchanged for a decade.

In PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial), McMurray et al. report that LCZ696, as compared with a target-dose enalapril-based regimen, significantly reduced the rates of death from any cause and from cardiovascular causes and the rates of hospitalizations for worsening heart failure in patients with a reduced ejection fraction. In addition, patients' quality of life, as measured on the Kansas City Cardiomyopathy Questionnaire, was significantly improved.[2]

Who were the patients in this remarkable trial, and how do they compare with the patients

Table 1. Mean Baseline Characteristics of Patients with Heart Failure and a Reduced Ejection Fraction in Five Trials.*

Trial	Age	Left Ventricular Ejection Fraction	NYHA Class	Heart Rate	Systolic Blood Pressure	Treatment			
						ACE Inhibitor or ARB	Beta-Blocker	Mineralo-corticoid Antagonist	ICD with or without CRT
	yr	%	*% of patients*	*beats/min*	*mm Hg*	*% of patients*			
AHEFT	57	24	95 in class III	NA	126	87	74	38	18
MADIT-CRT	65	24	85 in class II	NA	122	97	93	31	100
SHIFT	60	29	49 in class II; 50 in class III	79	121	91	89	60	5
EMPHASIS-HF	68	26	100 in class II	72	124	93	86	NA	20
PARADIGM-HF	64	<35 (in 88% of patients)	70 in class II; 24 in class III	72	121	100	93	56	15

* Shown are approximate estimates of mean values at baseline, as calculated from the available data, unless otherwise indicated. ACE denotes angiotensin-converting enzyme, AHEFT African-American Heart Failure Trial,[1] ARB angiotensin-receptor blocker, CRT cardiac resynchronization therapy, EMPHASIS-HF A Comparison of Outcomes in Patients in New York Heart Association (NYHA) Class II Heart Failure When Treated with Eplerenone or Placebo in Addition to Standard Heart Failure Medicines,[3] ICD implantable cardioverter–defibrillator, MADIT-CRT Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy,[4] NA not available, PARADIGM-HF Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial,[2] and SHIFT Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial.[5] The data for the MADIT-CRT study are from the initial report, with an average follow-up of 2.5 years.

enrolled in other noteworthy, successful trials in patients with heart failure (Table 1)[3-5]? The investigators included patients with New York Heart Association class II, III, or IV heart failure who had an ejection fraction of less than 40% (which was changed to 35% or less by an amendment to the protocol) and who were receiving the best available medical therapy. The patients who participated in PARADIGM-HF were similar to those in other studies involving patients with mild to moderately severe heart failure.[1-5]

Why did LCZ696 succeed in improving outcomes so convincingly in this representative population of patients? Drugs that inhibit the renin–angiotensin–aldosterone system (RAAS) have been foundational to cardiovascular drug therapy for almost three decades. RAAS inhibitors moderate vasoconstriction, myocyte hypertrophy, and myocardial fibrosis, an effect that has translated into clinically meaningful improvements in functional status and survival. Natriuretic peptides, which include atrial natriuretic peptide, B-type natriuretic peptide, and urodilatin, are secreted by the heart, vasculature, kidney, and central nervous system in response to increased cardiac-wall stress and other stimuli. Natriuretic peptides have potent natriuretic and vasodilatory properties, inhibit the RAAS, reduce sympathetic drive, and have antiproliferative and antihypertrophic effects as well.[6] Neprilysin inhibition results in an increased concentration of natriuretic peptides. Thus, the beneficial effects of RAAS inhibition are likely to be augmented by the enhancement of natriuretic peptide activity. LCZ696 is a fixed-dose combination of valsartan and AHU-377 (a neprilysin inhibitor prodrug) in a 1:1 ratio and is the first and most clinically developed agent in a new class of compounds.

Before random assignment in PARADIGM-HF, all patients had been receiving an angiotensin-converting–enzyme inhibitor or an angiotensin-receptor antagonist, in addition to their three to seven other cardiovascular drugs. The run-in phase of the trial ensured that all patients could maintain the dosing regimen, with the successive administration of enalapril (at a dose of 10 mg twice daily) and LCZ696 (at a dose of 200 mg twice daily). The authors report that 200 mg of LCZ696 delivers the equivalent of 160 mg of valsartan. Predictably, 12% of patients withdrew during the run-in phase because of an adverse event; withdrawal was more likely when patients were receiving enalapril than when they were receiving LCZ696. Although heart-failure guidelines suggest a target twice-daily administration of either 10 mg of enalapril or 160 mg of valsartan, numerous registries acknowledge that lower doses are commonly used in clinical practice. After randomization, fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of any adverse event (10.7% vs. 12.3%, P=0.03). Thus, LCZ696 was at least as well tolerated as target doses of enalapril in PARADIGM-HF.

The investigators report that as compared with baseline values, the mean systolic blood pressure at 8 months was 3.2±0.4 mm Hg lower in the LCZ696 group than in the enalapril group. They propose that this difference in blood pressure was not a determinant of the salutary benefits of LCZ696. Interestingly, neprilysin inhibition alone does not cause clinically important reductions in blood pressure, possibly because of neprilysin-dependent breakdown of polypeptide vasoconstrictors, such as angiotensin II.[7] In

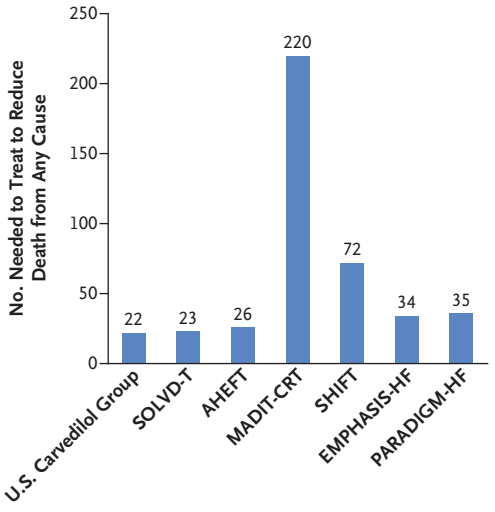

Figure 1. Numbers of Patients with Heart Failure Who Would Need to Be Treated to Reduce Any-Cause Mortality in Seven Clinical Trials.

SOLVD-T denotes Studies of Left Ventricular Dysfunction–Treatment.[9] The data for the MADIT-CRT study are from the initial report, with an average follow-up of 2.5 years.

a separate trial of LCZ696 in patients with heart failure and a preserved ejection fraction, there was no relationship between the blood-pressure effect and the natriuretic peptide level.[8]

PARADIGM-HF may well represent a new threshold of hope for patients with heart failure. Efforts to design novel pharmacotherapies that exploit our growing knowledge of pathophysiological pathways are increasingly coming to the clinical arena. The dual (or more) action of such drugs may translate into even greater long-term survival for patients (Fig. 1).[9,10] 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.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Perelman School of Medicine, University of Pennsylvania, Philadelphia.

This article was published on August 30, 2014, and last updated on September 17, 2014, at NEJM.org.

1. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57. [Erratum, N Engl J Med 2005; 352:1276.]
2. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
3. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11-21.
4. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
5. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85. [Erratum, Lancet 2010; 376:1988.]
6. von Lueder TG, Sangaralingham SJ, Wang BH, et al. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. Circ Heart Fail 2013;6:594-605.
7. Ruilope LM, Dukat A, Böhm M, Lacourcière Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet 2010;375:1255-66.
8. Jhund PS, Claggett B, Packer M, et al. Independence of the blood pressure lowering effect and efficacy of the angiotensin receptor neprilysin inhibitor, LCZ696, in patients with heart failure with preserved ejection fraction: an analysis of the PARAMOUNT trial. Eur J Heart Fail 2014;16:671-7.
9. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
10. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.

DOI: 10.1056/NEJMe1409898

A Call to Action for Acute Lymphoblastic Leukemia

Timothy A. Graubert, M.D.

The cure rates for precursor B-cell acute lymphoblastic leukemia (ALL) among children have improved, but the prognosis for older patients and children with relapsed disease remains poor. Risk stratification based on clinical features and disease characteristics can improve outcomes by enabling physicians to reduce the toxicity of therapy for patients with lower-risk disease and intensify therapy for patients with higher-risk disease. The negative prognosis associated with the t(9;22) translocation, which results in expression of the BCR–ABL1 activated kinase fusion protein, is attenuated by treatment that includes tyrosine kinase inhibitors, providing a paradigm for molecularly guided therapy in patients with precursor B-cell ALL. Several years ago, a subtype of precursor B-cell ALL was identified that shares a gene-expression profile with Ph-positive ALL (the term commonly used to describe ALL associated with the Philadelphia chromosome, which results from the t[9;22] translocation).[1,2] The pattern of gene expression in patients with Ph-like ALL prompted the hypothesis that other oncogenic drivers could substitute for BCR–ABL1, triggering a similar signaling cascade. Indeed, previous studies have identified rearrangements and mutations that activate cytokine receptor signaling in some cases of Ph-like ALL.[3,4]

In this issue of the *Journal*, Roberts et al.[5] define the frequency and genomic landscape of Ph-like ALL in a cohort of 1725 children and young adults with precursor B-cell ALL. They observed a marked rise in the proportion of Ph-like cases with age, from 12% among children to 27% among young adults (Fig. 1A). Nearly half (49.4%) of the young adults had either Ph-positive or Ph-like disease. The Ph-like cases were frequently found to be associated with *IKZF1* alterations (in 68% of patients with Ph-like ALL) and high *CRLF2* expression (in 47%), with the latter caused by genomic rearrangement in all