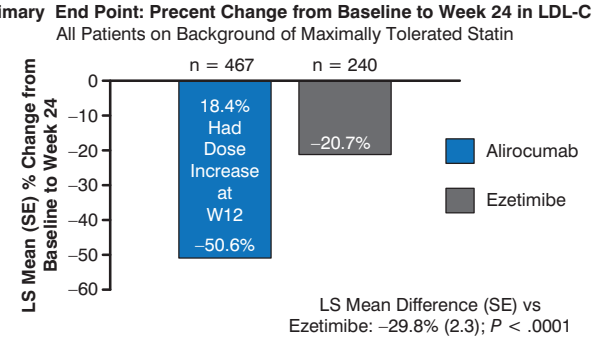
Figure 1. Effect of Alirocumab and Ezetimibe on LDL-C Levels at 24 Weeks



LDL-C, low-density lipoprotein cholesterol; LS, least squares (a statistical mean estimated from a linear model); SE, standard error.

Reproduced with permission from CP Cannon, MD.

Dr Cannon summarized that, in this population of patients with high CVD risk who were unable to achieve targets with maximal statin use, a treat-to-target approach with alirocumab (where ~80% of patients did not need to up-titrate the initial dose) allowed more than three-quarters of patients to achieve target LDL-C levels at week 24.

PARADIGM-HF: Novel Drug Reduced Outcomes, Improved Symptoms Better Than ACE Inhibition

Written by Mary Mosley

A greater reduction in cardiovascular (CV) death or heart failure (HF) hospitalization was achieved with an investigational drug, LCZ696, than with enalapril, an angiotensin-converting enzyme (ACE) inhibitor representing the gold standard treatment for HF that has been shown to reduce CV mortality in patients with HF with reduced ejection fraction (HFrEF) on top of optimal medical therapy in a large-scale, international, double-blind clinical trial. The trial was terminated early because of the improvement in CV death.

LCZ696 is an angiotensin receptor neprilysin inhibitor (ARNI), which combines a neprilysin inhibitor and the angiotensin receptor blocker (ARB) valsartan, to simultaneously counteract maladaptive mechanisms caused by degradation of vasoactive peptides by neprilysin and deficiencies in the endogenous adaptive elements in HF, stated Milton Packer, MD, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

The Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial [PARADIGM-HF; McMurray JJV et al. *N Engl J Med*. Published online August 30, 2014] randomized patients with clinically stable NYHA class II to IV HF, left ventricular ejection fractions (LVEFs) ≤40%, and modestly increased levels of brain natriuretic peptide (≥150 pg/mL) after a 2-week run-in phase to LCZ696 200 mg BID (n=4212) or enalapril 10 mg BID (n=4187). During the run-in, patients were switched from their current ACE inhibitor or ARB to enalapril 10 mg BID for 2 weeks, and then, to ensure tolerance of both drugs, LCZ696 was added at escalating doses (100 mg BID for 2 weeks, then 200 mg BID for 2 weeks).

The median follow-up period was 27 months, and the average daily doses at the last visit were LCZ696 375 mg and enalapril 18.9 mg. The patients were representative of patients with HF seen in the general community. They were aged 63.8 years, 22% were women, 60% had ischemic cardiomyopathy, and the LVEF was ~30%.

The results for the composite primary end point of CV death or HF hospitalization, for its components, and the secondary end point of all-cause mortality are detailed in Table 1. For all prespecified subgroups, LCZ696 was more effective than enalapril in reducing primary end point events and CV mortality.

Quality of life as measured by the Kansas City Cardiomyopathy Questionnaire at 8 months was significantly improved with LCZ696 versus enalapril ($P=.001$). There was no significant difference between the groups for new-onset atrial fibrillation (HR, 0.97; 95% CI, 0.72 to 1.31; $P=.84$) or protocol-defined decline in renal function (HR, 0.86; 95% CI, 0.65 to 1.13; $P=.28$).

Regarding safety, more patients in the enalapril group than the LCZ696 group discontinued treatment because of hypotension, hyperkalemia, or worsening renal function, and blinded, adjudicated angioedema was similar in the 2 groups (Table 2).

Dr Packer stated that LCZ696 was more effective than guideline-recommended doses of enalapril in patients with HFrEF to reduce all-cause mortality and CV death, the symptoms and physical limitations of HF, and the risk for HF hospitalization. LCZ696 was better tolerated and less likely to be discontinued because of an adverse event than enalapril. The rates of cough, hyperkalemia, and renal impairment were lower with LCZ696 than with enalapril, as was drug discontinuation for hypotension. The reduction in CV mortality with LCZ696 over enalapril was similar to that achieved when an ACE inhibitor is compared with placebo, indicating that LCZ696 doubles the effect of ACE inhibitors on CV death. These results provide robust support for using the novel drug instead of an ACE inhibitor or ARB, he stated.

Table 1. Outcomes for the Primary and Secondary End Points in PARADIGM-HF

Outcome	Enalapril (Number of Events)	LCZ696 (Number of Events)	HR	95% CI	*P* Value	Number Needed to Treat
CV death or HF hospitalization	1117	914	0.80	0.73 to 0.87	.0000002	21
CV death	693	558	0.80	0.71 to 0.89	.00004	32
HF hospitalization	658	537	0.79	0.71 to 0.89	.00004	NR
All-cause mortality	835	711	0.84	0.76 to 0.93	< .0001	NR

CV, cardiovascular; HF, heart failure; NR, not reported; PARADIGM-HF, Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

Table 2. Safety Outcomes in PARADIGM-HF

	LCZ696 (n = 4187)	Enalapril (n = 4212)	*P* Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< .001
Serum potassium > 6.0 mmol/L	181	236	.007
Serum creatinine ≥ 2.5 mg/dL	139	188	.007
Cough	474	601	< .001
Discontinuation for adverse event	449	516	.02
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized, no airway compromise	3	1	NS
Airway compromise	0	0	—

NS, nonsignificant; PARADIGM-HF, Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

NECTAR-HF: Cardiac Remodeling Not Reduced With VNS

Written by Mary Mosley

Vagal nerve stimulation (VNS) did not reduce the primary end point of cardiac remodeling at 6 months in patients who had heart failure (HF) with reduced ejection fraction in the first sham-controlled, double-blind clinical trial to evaluate this approach. The Neutral Cardiac Therapy for Heart Failure study [NECTAR-HF; Zannad F et al. *Eur Heart J.* 2014], led by Faiez Zannad, MD, PhD, Inserm, University of Lorraine, Lorraine, France, sought to determine whether an implanted VNS system would reset the altered autonomic nervous system balance found in HF. The 6-month data were presented, and follow-up will continue to 18 months.

NECTAR-HF researchers randomized patients who were receiving optimal medical therapy to a VNS system that stimulated the right vagal nerve with therapy turned on (therapy group; n = 63) or off (control group; n = 32). Criteria included the following: New York Heart Association (NYHA) class II to III HF, a left ventricular (LV) ejection fraction ≤ 35%, and LV end diastolic diameter ≥ 5.5 cm. The mean age of the patients was 59 years, most were men (therapy group, 89%; control group, 81%), and most had NYHA class III HF (51 and 22 patients, respectively). The number of patients who had an implantable cardioverter defibrillator, cardiac resynchronization therapy with defibrillation, or no device was 51, 5, and 7 in the therapy group and 22, 4, and 6 in the control group, respectively.

The 6-month safety results showed a similar number of events in each group. The infection rate was low at 7.4% (7 infections), the device was removed from 3 patients, and antibiotic treatment was used in 4 patients. The modified intention-to-treat analysis included 59 patients in the therapy group and 28 patients in the control group with paired data sets. After 6 months, therapy was turned on for all patients.

The primary end point of LV end systolic diameter was similar at baseline and at 6 months in the therapy group (4.9 cm for both) and control group (5.2 and 5.1 cm, respectively). The secondary end points evaluating cardiac remodeling were also similar at 6 months in both groups. The secondary end points of peak oxygen consumption and N-terminal pro–brain natriuretic peptide were similar in both groups at baseline and 6 months. More patients had an improvement