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

in their NYHA class in the therapy group versus the control group (62.1% vs 44.8%), while more patients in the control group versus the therapy group had worsening HF (10.3% vs 0.2%). The secondary end point measure of quality of life showed a significant improvement with therapy versus control for 2 functional questionnaires but not for the short form-36 mental health survey.

Regarding the improvement in symptoms and quality of life despite the lack of improvement in cardiac remodeling, Prof Zannad acknowledged that insufficient blinding may have contributed to the positive findings for the more subjective data. Although the primary echocardiography end point was blinded, many patients felt the stimulation (slight vibration in neck) and correctly guessed their assigned group.

This feasibility, proof-of-concept study did not demonstrate an improvement in its primary end point of cardiac remodeling with VNS. There were no safety concerns at 6 months. The trial design did support the use of sham control for further study of VNS and highlighted the need for sufficient blinding.

SIGNIFY: Treatment With Ivabradine Does Not Improve Outcomes and May Increase Risk in Patients With Angina

Written by Mary Mosley

Kim M. Fox, MD, Imperial College, London, United Kingdom, reported the results of the Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease Without Heart Failure [SIGNIFY; Fox K et al. *N Engl J Med*. 2014]. The study found that treatment with ivabradine did not reduce the risk of cardiovascular (CV) death or nonfatal myocardial infarction (NFMI). However, in patients with Canadian Cardiovascular Society (CCS) class II or greater angina at baseline, ivabradine increased the risk of CV death or myocardial infarction (MI).

The BEAUTIFUL study [Fox K et al. *Lancet*. 2008] also tested ivabradine in patients with stable coronary artery disease (CAD) and left ventricular systolic dysfunction. In the overall study population, the primary outcome of hospitalization for fatal and NFMI was not reduced with ivabradine versus placebo on top of standard therapy. However, ivabradine appeared to reduce the rate of the primary outcome in the patients with a heart rate ≥ 70 beats per minute (bpm). Ivabradine is currently approved in the European Union for use in patients with CAD and patients with heart failure and who are either intolerant of beta-blockers or are inadequately controlled despite treatment with beta-blockers.

SIGNIFY—a prospective, international, double-blind study—enrolled patients aged ≥ 55 years with stable CAD and ≥ 1 other CV risk factor, including CCS class ≥ II angina, a left ventricular ejection fraction (LVEF) > 40%, and a heart rate ≥ 70 bpm [Fox K et al. *N Engl J Med*. 2014], to further test the hypothesis that ivabradine improved outcomes in patients with elevated resting heart rate. A higher-dose regimen of ivabradine, a drug known to have a specific and direct effect on heart rate alone, was used to obtain maximum heart rate reduction in SIGNIFY. After a 14- to 30-day run-in, patients were randomized to ivabradine (7.5 mg, BID; n = 9550) or placebo (n = 9552), and the drug was uptitrated as tolerated to a maximum of 10 mg (BID) to obtain a target a heart rate of 55 to 60 bpm.

The study patients were mostly men (73%) aged 65 years with a LVEF (56%) and with a high frequency of prior MI (73%) and other risk factors. They were receiving optimal CV medical therapy [Gibbons RJ et al. *J Am Coll Cardiol.* 2003; Fox K et al. *Eur Heart J.* 2006]. The median follow-up was 27.8 months.

The baseline resting heart rate was 77 bpm in both groups. The mean reduction in heart rate was 9.7 bpm with ivabradine versus placebo. Prof Fox noted that the reduction in heart rate was less than what they had anticipated.

The incidence of the primary composite outcome of CV death or NFMI was similar with ivabradine (3.03% per year) and placebo (2.82%; $P = .20$), as was the incidence of its components (Table 1).

In the overall study population, the incidence of adverse events was higher with ivabradine versus placebo (73% vs 66.9%; $P < .001$). Symptomatic and asymptomatic bradycardia occurred in about 19% of patients

Table 1. Primary Outcome Results in SIGNIFY

	Percentage per Person-Year			
Outcome	Ivabradine	Placebo	HR (95% CI)	*P* Value
CV death or NFMI	3.03	2.82	1.08 (0.96 to 1.20)	.20
CV death	1.49	1.36	1.10 (0.94 to 1.28)	.25
NFMI	1.63	1.56	1.04 (0.90 to 1.21)	.60

CV, cardiovascular; NFMI, nonfatal myocardial infarction