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

Table 2. Primary Outcomes in Patients With CCS Class ≥ II Angina in SIGNIFY

Outcome	Percentage per Person-Year		HR (95% CI)	*P* Value
	Ivabradine	Placebo		
CV death or MI	3.37	2.86	1.18 (1.03 to 1.35)	.02
CV death	1.76	1.51	1.16 (0.97 to 1.40)	.11
Non-Fatal MI	1.72	1.47	1.18 (0.97 to 1.42)	.09

CCS, Canadian Cardiovascular Society; CV, cardiovascular; MI, myocardial infarction.

in the ivabradine group versus about 2.5% in the placebo group. Atrial fibrillation occurred in 5.3% and 3.8% of the ivabradine and placebo groups, respectively. Importantly, the total incidence of life-threatening arrhythmias—ventricular tachycardia, ventricular fibrillation, and Torsades de pointes—was infrequent (≤ 0.9%).

In the prespecified analysis of patients with angina CCS class ≥ II (n = 12 049), there was a significant increase of 18% in the composite of CV death and MI, and a similar nonsignificant trend was seen for the components of the primary outcome (Table 2). Prof Fox noted that this is the population in which the research group anticipated finding the maximum benefit with a lower heart rate.

In the angina population, ivabradine improved symptoms, with a greater improvement in CCS class at 3 months (24.8% vs 19.4% with placebo; $P < .01$). The need for elective coronary revascularization was not significantly reduced with ivabradine versus placebo (HR, 0.82; $P = .06$).

In summary, in the absence of clinical heart failure in patients with stable CAD, lowering the heart rate with ivabradine did not prevent the progression of CAD, stated Prof Fox, and in patients with angina at baseline, there was an increase in CV death or NFMI. The results of this study has led a review by the European Medical Agency that is ongoing to determine what, if any, further action is needed.

CONFIRM-HF: Novel Approach Treating ID Improved Function, Symptoms, and QOL

Written by Mary Mosley

A sustainable improvement in functional capacity, symptoms, and quality of life was shown in patients with symptomatic chronic heart failure (HF) and iron deficiency (ID) who were treated with intravenous (IV) ferric carboxymaltose (FCM) throughout 1 year, and this treatment may reduce the risk of hospitalizations due to worsening HF, stated Piotr Ponikowski, MD, Medical University, Wroclaw, Poland, who presented the results of A Study to Compare the Use of Ferric Carboxymaltose With Placebo in Patients With Chronic Heart Failure and Iron Deficiency [CONFIRM-HF; Ponikowski P et al. *Eur Heart J.* 2014].

ID is found in ≥ 50% of patients with HF, regardless of left ventricular ejection fraction (LVEF) or hospitalization status, and it is unrelated to the presence or absence of anemia. HF complicated with ID is associated with poor outcomes and increased mortality. The CONFIRM-HF trial was designed to determine the long-term sustainability of beneficial effects and safety and the potential impact of treatment with FCM on outcomes.

The double-blind trial conducted in 9 European countries randomized patients with NYHA class II and class III HF, LVEF ≤ 45%, brain natriuretic peptide (BNP) > 100 pg/ml, serum ferritin < 100 ng/ml or 100 to 300 ng/mL if transferrin saturation levels were < 20%, and hemoglobin < 15 g/dL to placebo (normal saline) or IV FCM. Blinding of patients was achieved by using black syringes and curtains, and there were blinded and unblinded clinical staff. In the correction phase, FCM (up to 2000 mg) was administered at baseline and week 6. In the maintenance phase, if ID was not corrected, FCM (500 mg) was administered at weeks 12, 24, and 36.

Of the 304 randomized patients, 150 in the FCM group and 151 in the placebo group comprise the full analysis set. The patients were representative of daily clinical practice: They were an average age of 70 years, 45% to 49% were women, around 50% were NYHA class II and III, and LVEF was approximately 37%. All patients were receiving optimal medical therapy for congestive HF. The mean ferritin level was 57 ng/mL, and close to 90% had a ferritin level < 100 ng/mL. The baseline 6-minute walk test (6MWT) distance was 288 m and 309 m in the FCM and placebo groups, respectively.

The primary end point of change in the 6MWT at week 24 was + 18 m with FCM and –16 m with placebo, resulting in an improvement of 33 m with FCM vs placebo (least squares mean; $P = .002$). At weeks 36 and 52, the 6MWT improved to an additional 42 m and 36 m, respectively, with FCM vs placebo ($P < .001$). The improvement in the primary end point was seen among all prespecified subgroups, representing the entire spectrum of HF, stated Prof Ponikowski.

The secondary end points measuring quality of life, including the Kansas City Cardiomyopathy Questionnaire and European Quality of Life 5D questionnaire, were improved early with FCM vs placebo and sustained at