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

week 52. Hospitalization due to worsening HF was significantly reduced with FCM compared with placebo.

The secondary end points of self-reported Patient Global Assessment (PGA) score and NYHA class improved early and were sustained at week 52. The odds ratio for PGA was >1 at week 6 and week 52 with FCM vs placebo (P=.29 and P=.001, respectively). The odds ratio for change in NYHA class was >1 at week 6 and week 52 (P=.067 and P<.001, respectively).

Dr Ponikowski concluded that treatment of iron deficiency with FCM in symptomatic HF patients resulted in sustained improvement in functional capacity, symptoms, and quality of life and resulted in a reduction in HF hospitalizations.

POPE-2: No Benefit With Colchicine to Reduce Persistent Postoperative Pericardial Effusion

Written by Mary Mosley

Postoperative pericardial effusion (POPE) is present within the first 7 days after cardiac surgery in 50% to 80% of patients, and the risk for early cardiac tamponade ranges from 0.5% to 1%. There is no drug that can treat this local hemorrhagic complication, stated Philippe Meurin, MD, Les Grands Prés, Villeneuve Saint Denis, France. From day 8, patients with POPE are at risk for persistence of the effusion, with the risk for tamponade dependent on its size. Although nonsteroidal anti-inflammatory drugs do not reduce persistent POPE, it is unknown whether the anti-inflammatory drug colchicine (COL) might be effective. COL has been shown to be effective in treating other pericardial conditions, including acute pericarditis [Imazio M et al. *N Engl J Med.* 2013] and postpericardiotomy syndrome [Imazio M et al. *Eur Heart J.* 2010].

The Colchicine Treatment for Post-operative Pericardial Effusion [POPE-2; NCT01266694] was a double-blind, placebo-controlled study to evaluate whether COL could reduce the volume of POPE. Conducted at 10 cardiac rehabilitation centers in France, the trial randomized 197 patients with moderate to large pericardial effusion (ie, grades II, III, and IV) on admission echocardiography (8 to 30 days after surgery) to a 14-day treatment course of placebo (n=99) or COL (n=99). The dose of COL was adjusted according to patient weight; all patients received 1 mg/day, except those who weighed ≥70 kg, who received an additional 1 mg on day 1. The primary end point was the change in mean pericardial effusion grade (MPEG) in the COL arm relative to placebo.

The patients has a mean age of 65 years, and most were men, 89% and 84% of the placebo and COL groups, respectively. At baseline, both groups were similar for the proportion of patients with grade II, III, and IV effusions and for MPEG.

Table 1. Primary End Point of Decrease in Mean Pericardial Effusion Grade

	Placebo Group	Colchicine Group	Mean Change (95% CI)	*P* Value
Baseline	2.9 ± 0.8	3.0 ± 0.8	NA	NA
Final	1.8 ± 1.3	1.7 ± 1.2	NA	NA
Change	−1.1 ± 1.3	−1.3 ± 1.3	−0.19 (−0.55 to 0.16)	.23

NA, not applicable.

The difference in the reduction of MPEG between the arms was not significant (Table 1).

Development of cardiac tamponade after 14 days of treatment did not significantly differ (log-rank P=.801) between the arms; neither did the requirement for pericardial drainage within 6 months (log-rank P=.202). The proportion of patients who had a ≥1-MPEG decrease was nonsignificant between the arms (67% and 74% of the placebo and COL groups, respectively; P=.27), as was the presence of atrial fibrillation at the end of the study (12% and 15%, respectively; P=.51). The reductions in the width of the echo-free space were similar at –4.7 and –5.8 mm in the placebo and COL groups, respectively (P=.23).

Furthermore, no difference was found with COL in any of the prespecified subgroups, including C-reactive protein level ≥30 mg/L and receiving an oral anticoagulant or in the per protocol analysis.

The POPE-2 study confirmed that a moderate to large POPE persisting >7 days is a serious condition, with cardiac tamponade occurring in 13 patients (6.6%) and pericardial drainage within 6 months occurring in 22 patients (11.2%) across both arms. COL did not provide any benefit either by echocardiography or on clinical events.

COPPS-2: Colchicine Reduced PPS in Cardiac Surgery Patients

Written by Mary Mosley

Colchicine (COL) administered perioperatively in patients undergoing cardiac surgery reduced the incidence of the primary end point of postpericardiotomy syndrome (PPS) compared with placebo. Secondary end points of postoperative atrial fibrillation (POAF) and postoperative pleural and pericardial effusions were not significantly reduced in an investigator-initiated,