

Clinical trials update from the European Society of Cardiology meeting 2014: PARADIGM-HF, CONFIRM-HF, SIGNIFY, atrial fibrillation, beta-blockers and heart failure, and vagal stimulation in heart failure

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Abstract

This article provides an overview of trials relevant to the pathophysiology, prevention, and treatment of heart failure, presented at the European Society of Cardiology meeting held in Barcelona in autumn 2014. Trials reported here include PARADIGM-HF (LCZ696 versus enalapril in heart failure), CONFIRM-HF (treatment of iron deficiency in heart failure), and SIGNIFY (ivabradine in patients with stable coronary artery disease). In addition, we discuss recent developments in the treatment of atrial fibrillation and the lack of benefit with the use of beta-blockers in these patients. Finally, the article describes recent advances in the use of vagal stimulation in patients with heart failure. © 2014 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of the European Society of Cardiology.

Keywords Randomized controlled trials; Heart failure; European Society of Cardiology 2014

Paradigm-HF

Presented by John McMurray from the University of Glasgow, UK

Paradigm-HF¹ was the most eagerly awaited of all the presentations at the European Society of Cardiology (ESC) this year. The medical treatment of chronic heart failure as a result of left ventricular systolic dysfunction has been one of the great successes of modern medicine, and the approach of triple therapy with beta-blocker, angiotensin converting enzyme inhibitor, and mineralocorticoid receptor antagonist has led to a halving of mortality from the condition. However, with the exception of ivabradine for some patients, there have been no great advances in standard medical treatment for many years.

LCZ696 is a combination of the angiotensin receptor antagonist (ARA), valsartan, and the neprilysin inhibitor, sacubitril. Neprilysin is the enzyme responsible for the breakdown of natriuretic peptides (as well as other vasoactive peptides), and so its inhibition causes a rise in these peptides. Previous studies of neprilysin inhibition in combination with ACE inhibitors have shown an excess of angio-oedema and no convincing evidence of a survival benefit: equally, the evidence in favour of using ARAs instead of ACE inhibitors has been equivocal.

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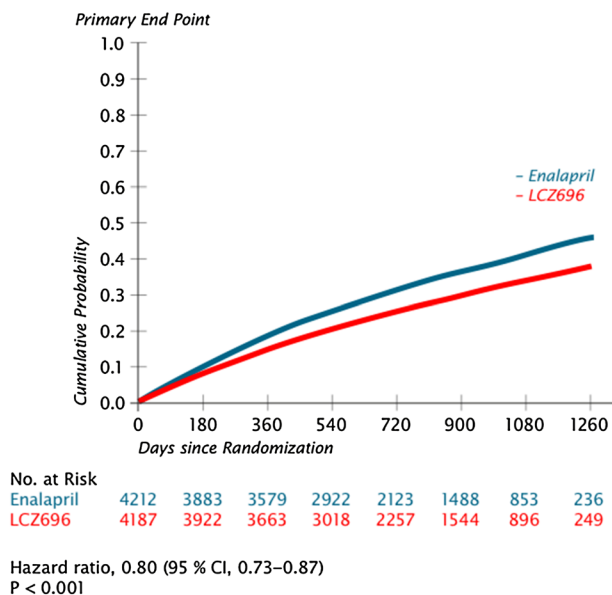


Figure 1 The primary end point (cardiovascular death or first hospitalization for heart failure) in PARADIGM-HF (taken from reference 1).

In PARADIGM-HF, 8442 patients with NYHA class II–IV symptoms were randomized to either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily), as well as other standard therapy. The average age of the patients was 64 years, 22% were women and 5% were black. The average left ventricular ejection fraction was just under 30%, and the cause of heart failure was ischaemic heart disease in 60%. Over 90% of patients were on a beta-blocker, and over half were on a mineralocorticoid receptor antagonist.

The trial was stopped early for overwhelming benefit in March, 2014 (Figure 1). The primary outcome (the composite of death from cardiovascular causes or hospitalization for heart failure) was reduced, with a hazard ratio of 0.8 for LCZ696 against enalapril. Both components of the end point were reduced, with, in addition, a reduction in all-cause mortality of 16%. LCZ696 also reduced the symptoms of heart failure more than enalapril.

There is no doubting the strength and robustness of the study design and conduct. LCZ696 is unequivocally superior to enalapril at the doses used. Some might argue that the dose of enalapril should have been 20 mg twice daily: this was the final dose target in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),² but 10 mg twice daily has been shown to improve mortality in Studies of Left Ventricular Dysfunction,³ and the average dose of enalapril achieved in the CONSENSUS study was, in fact, just under 10 mg twice daily.² It seems surprising that an agent that will increase the level of natriuretic peptide is helpful given that natriuretic peptide levels are already high in patients with heart failure. It may be,

however, that the beneficial effect of LCZ696 is mediated through an increase in other hormones

The results of PARADIGM-HF are likely to have a major impact on the future management of chronic heart failure. Whether it means that we should be offering wholesale change in therapy to all our patients with heart failure and reduced left ventricular ejection fraction is not yet clear and may depend, at least in part, on the price of the new drug once it has a name!

Confirm HF

Presented by Piotr Ponikowski, Wrocław Medical University, Poland

Patients with chronic heart failure are very commonly anaemic and, in turn, that anaemia is often because of iron deficiency.⁴ Further, many patients—perhaps as many as 40%—have iron deficiency, even in the absence of overt anaemia.⁵ Iron replacement therapy is an obvious potential treatment, and a previous study, FAIR-HF, suggested that intravenous iron carboxymaltose could improve patients’ symptoms and exercise capacity.⁶

The aim of CONFIRM-HF was to assess the benefits of long-term iron replacement therapy with intravenous iron carboxymaltose.⁷ Patients with iron deficiency (304), defined as serum ferritin level below 100 ng/mL, or between 100 and 300 ng/mL if transferrin saturation (TSAT) <20%, were eligible if their haemoglobin was less than 15 g/dL. Patients were randomized to receive iron carboxymaltose that was given using a schedule to achieve iron repletion followed by maintenance iron therapy if required for 1 year (where the last iron dosing could be at

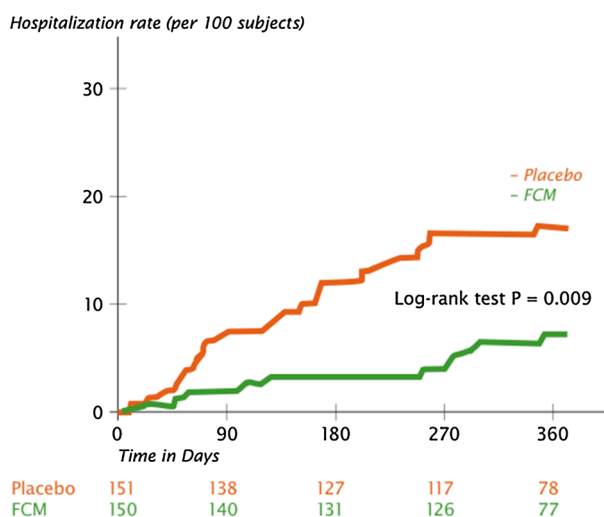


Figure 2 The secondary end point of time to first hospitalization as a result of worsening heart failure in CONFIRM-HF (taken from reference 7).

36 weeks). The primary end point was change in 6-min walk test (6MWT) distance from baseline to Week 24.

The average age of the patients was 69, and just under half were women. Average left ventricular ejection fraction was 37% with slightly more in NYHA class II than III. NT-proBNP was markedly raised at over 2000 pg/mL. Average haemoglobin was 12.4 g/dL; TSAT was 19% and ferritin was 57 ng/mL.

There was a significant increase in 6MWT with the difference between placebo and iron being 33 m ($P < 0.002$). The difference continued out to 1-year follow-up. There were significant improvements in fatigue score and quality of life (using the Kansas City Cardiomyopathy Questionnaire) with iron relative to placebo and a marked reduction in the composite of death or first hospitalization for worsening heart failure (Figure 2).

There are still many questions about iron replacement therapy. How to measure iron deficiency remains a problem: ferritin as an acute-phase reactant is an unreliable indicator, and directly measuring iron and TSAT is likely to be more robust. Whether different intravenous iron preparations differ in their biological effect is not clear—but ferric carboxymaltose certainly has the advantage that it can be very readily used with very low risk. Whether oral iron would have the same effect is not known. However, oral iron is often poorly tolerated and compliance is poor: intravenous repletion is reliable and robust.

A final worry is how far a given patient with iron deficiency should be investigated. Patients with heart failure are a population in whom bowel cancers are common: should they all have upper and lower gastrointestinal endoscopies if found to be iron deficient?

Signify

Presented by K Fox, Imperial College, Royal Brompton Hospital, London, UK

In patients with angina, heart rate slowing with ivabradine, the I_f inhibitor, results in a reduction in angina. The SHIFT trial added considerably to the weight of data suggesting that heart rate lowering was a good therapeutic target in patients with chronic heart failure who were in sinus rhythm. In SHIFT, ivabradine reduced the risk of cardiovascular death or hospital admission for worsening heart failure in patients with a resting heart rate of 70 per minute or higher. Ivabradine is increasingly being used for patients with heart failure and a resting heart rate over 70, and there was thus some concern in heart failure circles when the SIGNIFY trial was stopped earlier this year because of a signal that there might be harm associated with its use.

SIGNIFY was a trial involving 19 102 patients with stable coronary artery disease but no clinical heart failure and a heart rate of 70 beats per minute or more.⁸

Patients with angina limiting their activity (12,049) were included. Patients were randomized to receive ivabradine or placebo, titrated if needed to a dose of 10 mg twice a day to achieve a resting heart rate of 55–60. The composite primary end point was cardiovascular death or non-fatal myocardial infarction.

The mean age of the patients was 65, and 72.4% were men. The average resting heart rate was 77.2 beats per minute. Mean left ventricular ejection fraction was 56%. Patients (83%) were taking a beta-blocker, and just under 5% were taking a rate-limiting calcium antagonist. Ivabradine reduced the resting heart rate at 3 months by 10 beats per minute compared with placebo.

The trial was stopped early because of a small (but significant) increase in the primary end point in those with symptomatic angina (Canadian Cardiovascular Society class II–IV). However, the overall result in the total study population was neutral (hazard ratio for ivabradine, 1.08; $P = 0.20$) with, unsurprisingly, an increase risk of bradycardia with ivabradine (18.0 vs. 2.3% in the placebo group, $P < 0.001$).

It is a surprising finding. There is a huge body of epidemiological research showing that the risk of ischaemic cardiac events increases with increasing resting heart rate and evidence that reducing heart rate reduces that risk, particularly in patients with impaired left ventricular function. It may simply be that heart rate lowering is helpful in relieving angina symptoms, but that in patients with normal ventricular function, reducing heart rate is not beneficial in terms of prognosis. Another intriguing question was raised by Roberto Ferrari (University Hospital of Ferrara, Italy). The subgroup of patients who were also taking a rate-limiting calcium antagonist or strong inhibitor of the cytochrome P450, CYP3A4, had a higher risk of non-fatal myocardial infarction, suggesting that the risk may be associated with excessive heart rate lowering.

As far as managing patients with heart failure is concerned, however, the presentations at the ESC were reassuring: there is no suggestion of an increase in risk associated with ivabradine in patients with impaired left ventricular systolic dysfunction, and it can continue to be used with confidence in this population.

Atrial fibrillation, beta-blockers, and heart failure

Presented by Dipak Kotecha (University of Birmingham, UK)

Resting heart rate has become an important target in treating patients with heart failure in sinus rhythm, but it is less clear whether heart rate control has anything to offer patients with heart failure in atrial fibrillation⁹—who, after all, constitute around a quarter to a third of the population of patients with heart failure.

Dr Kotecha presented the results of an individual patient meta-analysis from 10 trials of beta-blockers in patients with heart failure as a result of left ventricular systolic dysfunction: trials had to include patients with a reduced ejection fraction, have at least 300 patients, include all-cause death as an end point, and have at least 6 months' follow-up. Of 18 254 patients, 3066 patients (17% of the total) had atrial fibrillation at baseline.¹⁰ The outcome was worse for patients in atrial fibrillation (21% died during 1.5 years' follow-up vs. 16% of those in sinus rhythm), but whilst beta-blockers were highly efficacious in reducing the risk of death for patients in sinus rhythm, they were not associated with any improvement in prognosis for patients with atrial fibrillation. The lack of benefit from beta-blockers was consistent across all subgroups of patients with atrial fibrillation studied, including age, sex, left ventricular ejection fraction, NYHA class, heart rate, and baseline medical therapy.

It is always difficult to extract data on subgroups from large trials to highlight groups that might not benefit. Nevertheless, the data are important and fit with other work suggesting that patients with atrial fibrillation behave differently to those in sinus rhythm. However, the findings do not translate into a 'ban' on beta-blockers for those in atrial fibrillation: rate control is often vital for symptom relief, and beta-blockers certainly appear safe in this meta-analysis. There is now a need for a randomized controlled outcome study of beta-blockers in patients with heart failure and atrial fibrillation.

Vagal stimulation in heart failure

There were two studies presented on vagal stimulation in patients with chronic heart failure. Chronic heart failure is associated with abnormal sympatho-vagal balance with increased sympathetic, and decreased parasympathetic, nervous system activity. Decreasing the sympathetic activity with beta-blockers is unequivocally helpful, but less is known about the effect of increasing parasympathetic activity. One possible approach is direct stimulation of the vagus nerve(s), the dominant source of parasympathetic innervation of the heart. A device similar in appearance to a standard pacemaker is implanted in a pre-pectoral pocket connected to a standard pacing lead positioned in the apex of the right ventricle. It is also connected to a stimulator cuff implanted around the vagus nerve in the neck.

(1) Inder Anand (University of Minnesota Medical School, USA) presented the results of the Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure, sponsored by Cyberonics.¹¹ Sixty

patients in India received a device to stimulate either the right ($n = 29$) or left ($n = 31$) vagus. Patients had NYHA class II or III symptoms and an average left ventricular ejection fraction of 32%. At 6 months, there was a 4.5% increase in LVEF and 4.1-mL decrease in LV end-systolic volume. There were no differences between left-sided and right-sided systems. There were increases in 6-min walk distance and improvements in quality of life.

A key problem in interpreting the results is the absence of a control group. The medical literature is bedevilled with modest-sized studies of interesting interventions, particularly of devices, that appear to show benefits, often in somewhat subjective end points, such as quality of life.

(2) Faiez Zannad (Université de Lorraine, Nancy, France) presented the results of Neural Cardiac Therapy for Heart Failure, sponsored by Boston Scientific.¹² Ninety-six patients were randomized 2:1 to receive the device, with the control subjects having the implantation but receiving no therapy. The sham procedure is vital to make sure that placebo effects are not interpreted as being signals of benefit. Patients had class II–III symptoms, had impaired left ventricular systolic function, and were in sinus rhythm.

There was no effect of the vagal stimulator on left ventricular end-systolic dimension, the primary end point of the study, or any other index of left ventricular remodelling. There was no effect on functional capacity assessed by peak oxygen consumption. There were improvements in quality of life and NYHA class, but these might be related to un-blinding: at least some patients could tell if they were receiving active treatment from the sensation in their necks.

At the moment, it is difficult to know what to make of vagal stimulation. It is a concern that the sham-controlled study demonstrated no significant effects, a problem with trials of devices previously where there can be a large placebo effect from device implantation alone. The Increase of Vagal Tone in Chronic Heart Failure trial¹³ aims to recruit up to 650 patients to a study comparing right-sided vagal stimulation to optimal medical therapy. Although it will have the problem of the lack of a sham-operated control group, the primary end point of all-cause mortality and heart failure hospitalization is likely to be free of a large placebo effect.

Declaration of interest

Professor Clark and Dr. Pellicori have no conflicts to declare.

References

1. McMurray JJ1, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. The PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
2. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435.
3. 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.
4. Witte KK, Desilva R, Chattopadhyay S, Ghosh J, Cleland JG, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? *Am Heart J* 2004;**147**:924–930.
5. Okonko DO, Mandal AKJ, Missouri CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relations to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011;**58**:1241–1251.
6. Anker SD1, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–2448.
7. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD; for the CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2014; doi:10.1093/eurheartj/ehu385, in press.
8. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R; the SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014; doi:10.156/NEJMoa1406430.
9. Cullington D, Goode KM, Zhang J, Cleland JG, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation? *JACC Heart Fail* 2014;**2**:213–220.
10. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD; on behalf of the Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet* pii: S0140-6736(14)61373-8. doi:10.1016/S0140-6736(14)61373-8. Epub ahead of print 2 Sept 2014.
11. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail* pii: S1071-9164(14)01189-0. doi:10.1016/j.cardfail.2014.08.009. Epub ahead of print 22 Aug 2014.
12. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Caste MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the neural cardiac therapy for heart failure (NECTAR-HF) randomized controlled trial. *Eur Heart J*;doi:10.1093/eurheartj/ehu345 pii: ehu345. Epub ahead of print 31 Aug 2014.
13. Hauptman PJ, Schwartz PJ, Gold MR, Borggrefe M, Van Veldhuisen DJ, Starling RC, Mann DL. Rationale and study design of the increase of vagal tone in heart failure study: INOVATE-HF. *Am Heart J* 2012;**163**:954–962.