Understanding and Treating Heart Failure

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Dialogues in Cardiovascular Medicine
In 1933, Sir Thomas Lewis believed that “the very essence of cardiovascular practice is the early detection of heart failure,” which he defined as “a condition in which the heart fails to discharge its contents adequately.” Since then, various other definitions for heart failure have existed and have evolved, as have advancements in treatments, based on our better understanding of the disease. The more modern definition from the European Society of Cardiology describes heart failure as an “abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures.”

In the UK, over 800,000 patients have heart failure, and it constitutes a large burden to the health care systems, costing close to £2 ($3) billion per year, with over 50% of the cost being from hospitalization for heart failure. With the aging population and rising prevalence of comorbidities, such as hypertension and diabetes mellitus, the burden of heart failure is expected to worsen with escalating costs. The prognosis of heart failure remains poor, with mortality being highest for those hospitalized. For example, in the 2013-2014 National Heart Failure audit in England, 30-day mortality for hospitalized patients was 15%, of whom, 10% had died in the hospital.

On a more positive note, there has been some progress made in improving prognosis, and much of this is associated with a better appreciation of the pathophysiology of heart failure, in particular the importance of blocking the overactivated renin-angiotensin-aldosterone and sympathetic nervous systems with angiotensin-converting enzyme inhibitors, β-blockers, and mineralocorticoid receptor antagonists. Furthermore, heart rate has been identified as an important modifiable risk factor that can be lowered to improve outcomes. These strategies have been particularly useful in patients categorized as having heart failure with reduced systolic function, resulting in reverse left ventricular remodeling and improved survival and quality of life. Unfortunately,
certain categories of heart failure, such as heart failure with preserved ejection fraction (HFPEF) or acute heart failure, progress has been limited in developing effective treatments that have a favorable impact on prognosis. There are multiple reasons that could explain this; for example, both HFPEF and acute heart failure are characterized by significant heterogeneity in patient populations, serving as a reason why trials of potential treatments have failed to be of benefit.

Other than pharmacological and device therapy, the value of safeguarding and empowering the heart failure patients by educating them about their disease and ensuring that multidisciplinary teams and technologies are available to help monitor, support, and reach out to these patients should not be underestimated, as these strategies also have significant prognostic impact. As our understanding of heart failure improves, we look to the future in an optimistic light, identifying potential treatment targets that can improve quality of life and survival.

In this important issue of Dialogues in Cardiovascular Medicine, edited by Ali Vazir, Frank Ruschitzka, the current president of the Heart Failure Association of the European Society of Cardiology, writes the lead article on understanding and treating heart failure, and offers a look into the future. He highlights the recent important advances in pharmacotherapy of heart failure with reduced systolic function with the angiotensin-neprylisin inhibitor sacubitril/valsartan, a new class of drug, which is associated with a 20% relative risk reduction in cardiovascular mortality compared with the angiotensin-converting enzyme inhibitor enalapril. This sort of advancement has not been achieved in a heart failure trial for at least a decade, especially when the comparator is an already established and effective treatment as opposed to the comparator being placebo. He also emphasizes the current challenges faced in managing HFPEF and acute heart failure syndromes, but he reports on the improved phenotyping and improved trial designs for new therapies that are on the horizon and are currently being investigated.

Jillian Riley is in a key position to discuss the multidisciplinary approach to managing heart failure and the important role of the heart failure nurse in the patient’s journey through acute admission, discharge, and patient education, follow-up, and monitoring, all of which are associated with better outcomes. She also discusses the role of the heart failure nurse in end of life care. Martin Cowie emphasizes the role, practicality, and effectiveness of telemonitoring in the management of the increasing elderly population living with heart failure. Finally, Andrew Morley-Smith, Carl Hayward, Sian Harding, and Alexander Lyon report on the stimulating area of gene therapy for heart failure, with the concept of replacing faulty genes with undamaged ones within the failing cardiomyocyte. They discuss the neutral findings of the CUPID-2 trial and the potential challenges in this translational field and look ahead to what is next in gene therapy for heart failure.
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In the last 25 years, evidence-based treatment algorithms in international HF guidelines have helped improve the management and treatment of HF by promoting the effective use of pharmacological and device therapies. However, the combination of aging populations and a marked rise in HF risk factors (i.e., hypertension, obesity, and diabetes) has meant that the morbidity, mortality, and economic burden of HF are set to rise. Fortunately, new evidence from clinical trials and molecular, cellular, genetic, and electronic research is providing promising new avenues to improve the treatment of HFPEF, HFREF, and acute HF. Examples of promising avenues include research on the pathophysiology of HFPEF and HFREF phenotypes, the improvement in HFREF prognosis with valsartan/sacubitril, and the development of novel drug and device therapies in acute and advanced HF. Cardiac metabolism and calcium cycling are exciting areas of HF research, and the replacement of cardiomyocytes using gene therapy, miRNA, and cell therapy holds great promise. In advanced HF, enhanced LVAD technology is making myocardial recovery a clinical objective. “The best way to predict the future is to invent it,” according to Alan Kay, an eminent American computer scientist. In HF, we have the interesting ideas and now the new tools to match.

**Understanding heart failure**

**DEFINITION OF HEART FAILURE**

In order to properly understand and effectively treat heart failure (HF), we must first define what it is. In HF, the heart is unable to pump enough blood to meet metabolic demand because of a diminished capacity for ventricular filling or ejection. 1,2 HF is an end stage of the cardiovascular disease continuum that is characterized by the symptoms of dyspnea, fatigue, and fluid retention and signs of elevated jugular venous pressure, pulmonary crackles, and displaced apex beat. 3

Over time, the quality of life of the HF patient worsens, functional capacity declines, and death may occur via pump failure or ventricular arrhythmias. In the years to come, the challenge of affordably managing HF will become a priority for many countries with aging populations. 1,2

Diagnosis of HF is based on history, physical examination, and investigation of a possible cardiac cause (as myocardial disease is usually responsible for systolic and/or diastolic ventricular dysfunction). The renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system are activated in HF, causing a range of deleterious effects, including myocardial injury. Many key HF treatments rely on the interruption of these two important systems. HF is normally seen in its chronic form, but the clinical course is punctuated by episodes of acute HF, which are marked by worsening signs and symptoms. The hearts of HF patients are particularly susceptible, with even minor upsets capable of provoking an episode of acute decompensation. 1,2

HF is commonly categorized according to whether ejection fraction (EF) is maintained (HF with preserved EF [HFPEF]), or not (HF with reduced EF [HFREF]). EF is widely used for classifying the diverse range of patients with HF—who differ with regard to demographics, comorbidities, prognosis, and treatment affinity. 1,2

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**Keywords:** acute; classification; device; genetics; pharmacotherapy; preserved ejection fraction; reduced ejection fraction; technology; therapeutic strategy

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Heart failure with reduced ejection fraction

HFREF can be defined as a combination of the usual HF symptoms and signs plus reduced LVEF, and it is often accompanied by LV enlargement with pathological ventricular remodeling (dilatation and reduced contractility). Those with LV systolic dysfunction regularly have elements of diastolic dysfunction as well. Coronary artery disease is the cause of half of the incident HF in the general population, but these are not the only risk factors.1,2,4 Untreated systolic dysfunction, which may be symptomless to begin with, deteriorates progressively due to additional myocyte death and neurohumoral activation in particular, leading to increased LV enlargement and a reduction in EF.1,2 Compared with HFPEF patients, HFREF patients are younger, more likely to be men, and less likely to be obese. Importantly, the prognosis of patients with HFREF is worse than that of HFPEF patients.

Heart failure with preserved ejection fraction

The diagnostic criteria proposed by the Heart Failure Associations of the European Society of Cardiology to define the syndrome of HFPEF share three features: (i) clinical signs or symptoms of HF, (ii) evidence of normal LV systolic function, and (iii) evidence of abnormal LV diastolic dysfunction. Patients with HFPEF have the usual symptoms and signs of HF, but unlike HFREF, there is no LV dilation and LVEF is unaffected or only mildly impaired. Structural heart disease, like LV hypertrophy or left atrial enlargement, and/or diastolic dysfunction (determined by Doppler echocardiography or cardiac catheterization), may be present.1,2 HF estimates indicate that about half of HF patients have HFPEF, and its incidence appears to be on the rise. While the number one cause of HFPEF is hypertension, other causes, such as obesity, diabetes mellitus, hyperlipidemia, and atrial fibrillation, are also often observed in HFPEF. Some HFPEF patients will have previously had HFREF, and the clinical characteristics of this group are different from those of patients who have only ever had HFREF or HFPEF,1,2 highlighting the obvious need for standardization of diagnostic criteria and, in particular, the choice of EF cut-off levels for the definition of HFPEF and HFREF.

Acute heart failure

The term “acute heart failure” describes HF symptoms and signs that occur or change suddenly. Episodes of acute HF are frequently triggered by a cardiac abnormality, such as an arrhythmia in HFREF or severe hypertension in HFPEF. Despite the “acute” label, the severity and duration of presenting symptoms vary considerably.1,2 Immediate medical attention and urgent hospital admission are required. In the short term, the principal objectives are to improve symptoms and stabilize hemodynamic status; in the long term, focus shifts toward the prevention of recurrences and improvement in prognosis.

Epidemiology of heart failure

Globally, nearly 40 million patients have a diagnosis of HF. Global population aging means the burden of HF is likely to get worse, even in low- to middle-income countries where hypertension, obesity, and diabetes caused by sedentary Western lifestyles has begun to impact population health.5-7 One negative upshot of the improved treatment of early cardiovascular disease in recent years is the increased manifestation of late-
stage cardiovascular disease, like HF. The prevalence of HF rises with age, growing from 1%-2% in the adult population to ≥10% in those ≥70 years. The prevalence of asymptomatic LV dysfunction (systolic or diastolic) also rises with age, and estimates vary from 6% to 21%. After the age of 40, the lifetime risk for Americans of developing HF is 20%.1,2

Hypertension, diabetes mellitus, metabolic syndrome, and atherosclerotic disease are all common risk factors for HF. Treatment of risk factors is valuable: anti-hypertensive treatment halves the risk of HF, while treatments that target components of metabolic syndrome—such as diabetes mellitus, hypertension, and dyslipidemia—reduce the risk of developing HF.3,4 Treatments even exist for recently discovered HF risk factors, such as elevated heart rate.9,10 In the US, the annual expenditure on HF surpasses $30 billion, with over half of these costs spent on hospitalizations.11 Most HF patients (83%) have been hospitalized and many (43%) have been hospitalized several times (≥4 times). Up to 1 in 4 patients hospitalized for HF will be rehospitalized within 1 month.1,2

CAUSES OF HEART FAILURE

Heart failure is a progressive clinical syndrome with numerous etiologies. In the ESC-HF Long-Term Registry, a prospective, observational study conducted in 211 cardiology centers in 21 European and Mediterranean countries, ischemic etiology accounted for 43% of the cases in patients with chronic HF.12 Less common, but important, causes of HF in order of decreasing prevalence are cardiomyopathies, infections, particularly viral myocarditis as well as alcohol, and cytotoxic drugs.

COMORBIDITIES IN HEART FAILURE

Diabetes

A wealth of new findings on HF comorbidities, such as diabetes, has helped build a new understanding about the relationship between these comorbidities and HF. Diabetes is highly prevalent in HF and its presence is linked with a negative prognosis. Albeit that HF itself may lead to insulin resistance through sympathetic nervous system activation, systemic blood flow impairment, and skeletal muscle mass reduction and a consequential sedentary lifestyle, regulatory agencies today now routinely demand information about the cardiovascular safety of new antidiabetic agents. While the first-line antidiabetic agent metformin is now regarded to be relatively safe in HF, the safety of other antidiabetics in HF is a matter of ongoing debate. In particular, glitazones and some sulfonylureas may increase sodium and water retention and subsequently may increase the risk of HF. Similarly, the dipeptidyl peptidase 4 inhibitors (DPP-4) came under scrutiny after saxagliptin was found to increase HF hospitalizations by 27% without demonstrating other cardiovascular benefits in SAVOR TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction).13 Interestingly, another DPP-4 inhibitor, sitagliptin, did not increase HF hospitalizations, but failed to demonstrate cardiovascular benefit. In the EXAMINE trial (EXAMINation of cardiovascular outcomes with alogliptin vs standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome),14 there was a nonsignificant signal for an increased risk of HF with another DPP-4 inhibitor, alogliptin, in diabetic patients with acute coronary syndrome.15

The TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) showed that the DPP-4 inhibitor sitagliptin did not increase the incidence of HF vs control treatment (HR, 1.00; 95% CI, 0.83-1.20; P=0.98) in 14,671 patients with type 2 diabetes mellitus, cardiovascular disease, and a baseline HbA1c of 6.5% to 8% after 3 years.16 There was no difference (HR, 0.98; 95% CI, 0.88-1.09; P<0.001 for noninferiority) in the composite end point (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke or hospitalization for unstable angina). Taken together, although a DPP-4 inhibitor class effect can be discounted on the basis of these results, ongoing vigilance is warranted for this class.

The recent EMPA-REG OUTCOME trial (EMPAgliflozin cardiovascular OUTCOME event trial in type 2 diabetes mellitus patients) analyzed the effects of the sodium-glucose cotransporter 2 inhibitor empagliflozin vs placebo on the rate of the primary composite cardiovascular outcome and death from any cause when added to standard care in patients with type 2 diabetes at high risk for cardiovascular events.17 After 3.1 years, the primary end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (HR, 0.86; 95% CI, 0.74-0.99; P=0.04) and the secondary end point (hospitalization for heart failure) (~35%; P=0.002) were significantly reduced empagliflozin.15

Depression

Sertraline did not reduce depression or improve cardiovascular status in HF patients with depression compared with placebo in the SADHART-CHF trial
(Sertraline Against Depression and HeART disease in Chronic Heart Failure). After 12 weeks, there was no between-group difference in the cardiovascular profiles of patients (worsened, improved, or unchanged) 29.9%, 40.6%, and 29.5% for sertraline vs 31.1%, 43.8%, and 25.1% for placebo \( (P=0.78) \). In HFREF patients with major depression in the MOOD-HF trial (MOrbidity, mOrtality and mood in Depressed Heart Failure patients), escitalopram did not reduce mortality or hospitalizations, nor did it reduce depression symptoms, compared with placebo. Selective serotonin reuptake inhibitor (SSRI) antidepressants should be used in HFREF patients with caution, as in further analyses, mortality and hospitalization improved with escitalopram in patients with milder HF, but worsened in those with more severe HF. Depression may well be a natural byproduct of HF and, with the resolution of HF symptoms, depression may disappear of its own accord. It may already be alleviated by regular patient contact, since depressive symptoms diminished over time with placebo and SSRIs in both trials. 18,19

**Dyslipidemia**

The CORONA (COntrolled ROsuvastatin in multINA-tional trial heart failure) and GISSI-HF (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardi-co-Heart Failure) trials showed that rosuvastatin did not reduce mortality or coronary events in HFREF patients. 20,21 All the patients from CORONA and most from GISSI-HF had HF of ischemic origin. Rosuvastatin lowered the number of repeat HF hospitalizations in a recent reanalysis of CORONA. One explanation is that cholesterol may counteract the deleterious effects of endotoxin in HF.

**Sleep-disordered breathing**

Half of HF patients have sleep-disordered breathing, which includes Cheynes-Stoke respiration, obstructive sleep apnea, and central sleep apnea. 22 Central sleep apnea is associated with HF severity, mortality risk, and ventricular arrhythmias. 23 A trial of continuous positive airway pressure in central sleep apnea in HFREF patients found no evidence of outcome benefits, 24 so attention turned to adaptive servo-ventilation (ASV).

New findings show, however, that adding ASV to positive airway pressure is detrimental in HFREF patients with central sleep apnea. 25 The SERVE-HF trial (treatment of sleep-disordered breathing with predominant central sleep apnea with adaptive SERvoVentilation in patients with chronic Heart Failure) in 1325 patients with moderate to severe HF, LVEF <45%, and predominant central sleep apnea showed that HF patients treated with an ASV device on top of expiratory positive airway pressure were at a greater risk of cardiovascular death than control patients (HR, 1.34, 95% CI, 1.09-1.65, \( P=0.006 \)). There was also a trend toward more cases of all-cause mortality and HF hospitalizations. Mortality risk increased as HF severity increased. If central sleep apnea is a compensatory mechanism, ASV may cause interference leading to problems. Alternatively, in certain sensitive HF patients positive airway pressure may worsen cardiac function. Phrenic nerve stimulation is currently under investigation as a way of reducing Cheynes-Stokes respiration.

**Gout**

Uric acid levels are frequently elevated in HF patients, predict outcome, and correlate with gout risk, and it has been speculated that increased xanthine oxidase might affect the pathophysiology of HF. However, two studies in HFREF, EXACT-HF (xanthine oxidase inhibition for hyperuricemic heart failure patients) with allopurinol and OPT-CHF (OxyPurinol Therapy for Congestive Heart Failure) with oxypurinol, 26,27 failed to show the benefit of xanthine oxidase inhibition on HF outcomes. In EXACT-HF, treatment with allopurinol did not improve the clinical status of HF patients compared with placebo (worsened, unchanged and improved) 45%, 42%, and 13% for allopurinol vs 46%, 34%, and 19% for placebo, respectively, \( P=0.68 \) after 24 weeks. Similar findings were obtained in OPT-CHF: treatment with oxypurinol did not improve the clinical status of HF patients after 24 weeks. One reason may be that diminishing uric acid levels reduces a beneficial antioxidant effect. Nevertheless, treatment of gout in certain types of HFREF patients may be worthwhile.

**Iron deficiency**

Intravenous iron improved the symptoms, functional capacity, and quality of life of 304 iron-deficient HFREF patients, regardless of anemic status, in the CONFIRM-HF trial (COnparisoN of the use of Ferric carBoxymaltose with placebo in patients with chronic Heart Failure and iron deficiency), a double-blind, placebo-controlled trial. 28 Patients in CONFIRM-HF were randomized to treatment with iv ferric carboxymaltose or placebo for 52 weeks. Intravenous iron also reduced the risk of hospitalization for worsening HF (HR, 0.39, 95% CI, 0.19-0.82, \( P=0.009 \)). Over a third (40%) of HFREF patients are iron deficient, and iron deficiency is asso-
associated with increased symptom severity and outcomes. CONFIRM-HF corroborated the results of the FAIR-HF trial (Ferric carboxymaltose Assessment in patients with IRon deficiency and chronic Heart Failure). Neither study, however, was able to show an effect on mortality because of their relatively small sizes.

PROGNOSIS

HF mortality has declined in the last quarter of a century from 60%-70% within 5 years of diagnosis to less than 50%. Mortality rates after HF hospitalization in the US in the ARIC study (Atherosclerosis Risk In Communities) were 10.4%, 22%, and 42.3% after 30 days, 1 year, and 5 years, respectively. Severe HF has a poor prognosis. The 5-year mortality rate of HF patients increases with the severity of HF (3%, 4%, 25%, and 80% for stages A, B, C, and D, respectively), with survival declining rapidly in the later stages of HF. About 1 in 5 patients hospitalized for HF die. Prognosis in HF is influenced by age, cause of HF, New York Heart Association (NYHA) class, EF, comorbidities (renal, diabetic, anemic, or hyperuricemic), and natriuretic peptide.

Current therapeutic strategies and targets for treating heart failure

Nonpharmacological

Exercise and the multidisciplinary management are recommended as part of the holistic management of chronic HF; the former has been shown to improve the functional capacity and symptoms of HF patients, while the latter has been shown to reduce the risk of hospitalization for HF.

TREATMENT OF HFREF

Pharmacological

Modern international HF guidelines provide a robust evidence-based framework to direct prescribing in HF. Current guideline-recommended pharmacological therapy of HFREF is effective at achieving the objectives of both clinicians and patients. For clinicians, these aims include the relief of symptoms and signs, prevention of hospitalization, and mortality reduction. Symptom relief is also important from a patient’s perspective, but so too are quality of life and functional capacity. Indirectly, the pharmacological control of HF risk factors is relevant and it should not be forgotten. Standard systolic HF treatments that block neurohor-
monal pathways include ACE inhibitors (or angiotensin receptor blockers [ARBs]), β-blockers, and mineralocorticoid receptor antagonists (MRAs). Diuretics are also regularly prescribed alongside these to reduce congestive symptoms and signs. Better outcomes are obtained with higher doses, but in clinical practice titration to these target doses is challenging. Loop diuretics are popular in HF, but in patients with concomitant hypertension, particularly inpatients with a GFR >40 mL/min, thiazide diuretics may be more appropriate.

All the main HFREF treatments improve prognosis. ACE inhibitors reduce the risk of death and hospitalization in all HFREF patients, regardless of the severity of HF symptoms. Treatment with β-blockers in HFREF can markedly improve EF, eliminate symptoms, and decrease the risks of all-cause mortality and combined all-cause mortality and hospitalization. It appears beneficial regardless of coronary artery disease or diabetic status, race, sex, or treatment with ACE inhibitors. β-Blockers do not, however, improve prognosis in HF patients with atrial fibrillation. A pooled analysis comparing β-blockers with placebo in HFREF in 18254 patients found that β-blockers reduced all-cause death (by 27%) in HFREF patients in sinus rhythm (HR 0.73; 95% CI, 0.67-0.80; P<0.001), but not in those with atrial fibrillation (n=3066; HR, 0.97; 95% CI, 0.83-1.14; P=0.73).

As regards outcome reduction with MRAs, all-cause mortality was reduced by 30% (RR, 0.70; 95% CI, 0.60-0.82; P<0.001) after 24 months with spironolactone vs placebo in 1663 HFREF patients with LVEF <35% in the RALES study (Randomized Aldactone Evaluation Study). Decreases in sudden cardiac death (RR, 0.71; 95% CI, 0.54-0.95; P=0.02) and worsening HF hospitalizations (RR, 0.65; 95% CI, 0.54-0.77; P<0.001) were also observed in this trial. In a more diverse range of HFREF patients, eplerenone, another MRA, reduced all-cause mortality, cardiovascular mortality, and HF hospitalization.

Hyperkalemia can be a limiting factor for the use of MRA blockade in HFREF. Spironolactone and eplerenone can concentrate in the kidney, increasing local concentrations of potassium. Finerenone, a nonsteroidal MRA distributed more equally in the heart and kidney, increased potassium levels less than spironolactone with no difference in myocardial wall stress between the two agents. Finerenone is also currently being compared with eplerenone in a phase 2b study. Two short-term studies showed that sodium zirconium cyclosilicate and patiromer reduced elevated potassium in hyperkalemic patients by binding potassium in the gastrointestinal tract, but their safety and efficacy in HF still need to be determined.

ACE inhibitors and MRAs (and probably ARBs) are useful in HF patients with moderate (stage 3) kidney disease (eGFR, 30-59 mL/min/1.73 m²), while limited evidence suggests ACE inhibitors and ARBs may be useful in HF patients with severe kidney disease (eGFR, <30 mL/min/1.73 m²). The resolution of venous congestion and prevention of HF decompensation by neurohumoral blockers helps preserve renal function.

Other treatments in systolic heart failure
Some drugs have proven useful for reducing symptoms and/or HF hospitalizations, despite a lack of evidence for an effect on all-cause mortality. The addition of ARBs to standard HF therapy has been shown to reduce the risk of hospitalization for HF by 24% in the Val-HeFT trial (Valsartan Heart Failure Trial) and 17% in the CHARM-Added trial (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity–Added) making ARBs a useful alternative in patients unable to take an ACE inhibitor. ARBs also improved symptoms and quality of life in CHARM and Val-HeFT.

Heart rate is an independent prognostic factor in HF patients. Ivabradine inhibits the If channel in the sinus node leading to heart rate reduction in HF patients in sinus rhythm. In the SHIFT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial), the addition of ivabradine to standard HF treatment (including β-blockers) in symptomatic patients with LVEF ≤35% and heart rate ≥70 bpm led to a reduction in the primary composite end point of cardiovascular death or hospital admission for worsening HF (HR, 0.82; 95% CI, 0.75-0.90; P=0.001) after 22.9 months. Substantial reductions in hospital admission for worsening HF (HR, 0.74; 95% CI, 0.66-0.83; P<0.0001) and HF death (HR 0.74, 95% CI, 0.58-0.94; P=0.014) were important contributors to the reduction in the primary end point.

Digoxin can be used in symptomatic HF patients in sinus rhythm with LVEF ≤40%. Although it did not reduce all-cause mortality vs placebo in the DIG trial (Digitalis Investigation Group), it did reduce the risk of hospitalization for worsening HF by 28% (RR, 0.72; 95% CI, 0.66-0.79; P<0.001). Digoxin is also a second-line alternative to β-blockers for reducing an elevated ventricular rate in patients with symptomatic HFREF and atrial fibrillation. In African-Americans patients
with HF, adding a combination of hydralazine and isosorbide dinitrate to standard HF therapy, including ACE inhibitors, β-blockers, and MRAs, not only improved symptoms, but reduced morbidity and mortality as well. Nevertheless, concerns about the study size and early termination have limited the impact of these results.\(^1\)

GISSI-HF demonstrated that omega-3 polyunsaturated fatty acids have a slight treatment effect vs placebo on all-cause mortality (adjusted HR, 0.91; 95% CI, 0.83-1.00, \(P = 0.041\)), but no effect on HF hospitalization.\(^{50}\)

Nonrecommended treatments

Certain treatments cannot be recommended because either there is no proof of benefit or, worse still, outright proof of harm. Treatment in HFREF with statins, renin inhibitors, and oral anticoagulants lacks proof. Treatment with thiazolidinedione, calcium channel blockers, nonsteroidal anti-inflammatory drugs, and COX-2 inhibitors, or the addition of an ARB or direct renin inhibitor to treatment with an ACE inhibitor and MRA, should be avoided as they can be harmful.\(^1\)

Devices

Implantable cardioverter-defibrillator

Ventricular arrhythmias (and occasionally bradycardia and asystole) are responsible for much of the sudden death of HF patients, in particular those with less severe symptoms. Prevention of sudden death, which accounts for half of HF deaths, is an important HF objective. Although certain drugs can reduce the risk of sudden death in HF, they do not eliminate it entirely. Therefore, implantable cardioverter-defibrillators (ICDs) are invaluable for reducing the risk of ventricular arrhythmia–related mortality.\(^1\)

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) is useful in symptomatic HF patients by enhancing ventricular contractility, diminishing secondary mitral regurgitation, reversing ventricular remodeling, and sustaining improvement in LVEF. Patients with prolonged QRS (≥150 ms) should receive CRT if they are in sinus rhythm, their LVEF is low (≤30%), and they have a good functional status. Evidence for CRT is robust in left bundle branch block, but less so in right bundle branch block, intraventricular conduction delay, or atrial fibrillation.\(^1\)

Length of QRS prolongation is an important determinant of which patients might benefit from CRT. In the EchoCRT trial (ECHOcardiography guided Cardiac Resynchronization Therapy),\(^{51}\) CRT therapy has been found to increase all-cause mortality in HFREF patients with a QRS <130 ms and signs of left ventricular dyssynchrony (HR, 1.81; 95% CI, 1.11-2.93; \(P = 0.02\)); guidelines recommend against using CRT with a QRS <120 ms. A meta-analysis in 3782 HFREF patients has suggested a QRS cut-off >140 ms,\(^{52}\) a suggestion supported by a subanalysis of EchoCRT that showed CRT was of no value in patients with a QRS of 120-130 ms.\(^{53}\)

A reduction in HF events helped CRT significantly reduce all-cause death or HF compared with ICD therapy in 1820 patients with mild HFREF (NYHA classes I-II), QRS ≥130 ms, and LVEF ≤30% in the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) after 2.4 years.\(^{54}\) Mortality was significantly reduced by 41% after 5.6 years in HFREF patients with left bundle branch block (adjusted HR, 0.59; 95% CI, 0.43-0.80, \(P < 0.001\)), but not in those without.\(^{55}\)

TREATMENT OF HFPEF

HFPEF is currently treated based on observation and experience, as there are no treatments that reduce morbidity and mortality in HFPEF.\(^{1,2}\) Drugs that work in HFREF do not necessarily work in HFPEF and, worryingly, the prevalence of HFPEF is increasing. In HFPEF, the relief of congestion and myocardial ischemia and the reduction in blood pressure (and ventricular rate in atrial fibrillation) are important objectives. Like in HFREF, diuretics can be used to alleviate breathlessness and edema. Unlike HFREF, calcium channel blockers that lower heart rate, like verapamil, are useful in HFPEF by helping relieve symptoms and enhancing exercise capacity. They also decrease raised blood pressure, relieve myocardial ischemia, and, like β-blockers, control ventricular rate in atrial fibrillation patients. Apart from heart-rate–lowering calcium channel blockers, if a drug is unsuitable in HFREF it is also unsuitable in HFPEF.\(^1\) Nonpharmacological treatment approaches should not be ignored, as exercise and weight control can improve diastolic function and physical performance in HFPEF patients.

As mentioned above, therapies shown to be of benefit in HFREF have failed to do the same in HFPEF, including ARBs, ACE inhibitors, and most recently MRAs. Treatment with spironolactone was unable to reduce the primary end point of cardiovascular death, HF hospitalization, and aborted cardiac arrest vs placebo (HR, 0.89; 95% CI, 0.77-1.04, \(P = 0.14\)) in 3445 HFPEF patients over 3.3 years in the TOPCAT trial (Treatment Of Preserved CArdiac funkTion heart failure with an
aldosterone antagonist). A component of the primary end point, HF hospitalization, was reduced with spironolactone (HR, 0.83; 95% CI, 0.69–0.99; \(P=0.04\)). The results do not preclude the possibility that spironolactone may be useful in HF patients with mildly reduced ejection fraction.

Combining treatments is no guarantee of reducing outcomes in HFPEF either. When an ARB was added to treatment with ACE inhibitors and/or β-blockers in HFPEF patients in the SUPPORT trial (SUPplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using OlmesarTan), cardiovascular risk and the risk of renal dysfunction increased. In this trial, the ARB olmesartan was added to ACE inhibitors, β-blockers, or both. Mean ejection fraction was 54% in the 1147 patients enrolled. The primary end point (all-cause death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for worsening HF) did not differ significantly (HR, 1.18; 95% CI, 0.96–1.46; \(P=0.11\)). Outcomes were worse when olmesartan was added to patients on both ACE inhibitors and β-blockers: the primary end point (HR, 1.47; 95% CI, 1.11–1.95; \(P=0.006\)), all-cause death (HR, 1.50; 95% CI, 1.01–2.23; \(P=0.046\)), and renal dysfunction (HR, 1.85; 95% CI, 1.24–2.76; \(P=0.003\)) all increased.\(^{15}\)

Success has also eluded other approaches to the treatment of HFPEF. In HFPEF, decreased bioavailability of nitric oxide leads to decreased cyclic guanosine monophosphate (cGMP) levels in myocytes. The RELAX study (SeRELAXin in acute heart failure patients with preserved left ventricular ejection fraction) was unable to show any benefit of treatment with the phosphodiesterase type 5 inhibitor sildenafil in 216 elderly HFPEF patients compared with placebo.\(^{58}\) No improvement was observed in maximal exercise capacity (\(P=0.90\)), 6-minute walking distance (\(P=0.92\)), clinical status (\(P=0.85\)), quality of life, left ventricular remodeling, or diastolic function after 24 weeks of follow-up.\(^{15}\) Another study that compared sildenafil in 52 patients with HFPEF and pulmonary hypertension failed to find a difference in pulmonary artery pressure, the primary end point (\(-2.4\) vs \(-4.7\) mm Hg; \(P=0.14\)), or other invasive hemodynamic or clinical parameters after 12 weeks.\(^{59}\) Some treatment benefits were obtained using a different approach focusing on cGMP production rather than preventing degradation. Although treatment with soluble guanosine cyclase stimulator riociguat did not reduce mean pulmonary artery pressure vs placebo in 21 HFPEF patients (\(P=0.6\)), it did improve other hemodynamic and echocardiographic parameters like stroke volume (+9 mL; 95% CI, 0.4–17; \(P=0.04\)), systolic blood pressure (\(-12\) mm Hg; 95% CI, \(-22\) to \(-1\); \(P=0.03\)), and right ventricular end diastolic area (\(-5.6\) cm\(^2\); 95% CI, \(-11\) to \(-0.3\); \(P=0.04\)).\(^{60}\)

It is now becoming clearer just how different HFPEF and HFREF are. Studies that help improve our understanding of its pathophysiology and that give us a clearer idea of the phenotype of HFPEF patients are vital next steps. Coronary artery disease and mechanical dysynchrony, for example, are found more commonly in HFPEF patients than the general population. The need for better characterization of different HFPEF phenotypes was illustrated by the difference in primary end point reduction between HFPEF patients from the Americas and those from Georgia and Russia in TOPCAT. Specific HFPEF diagnostic criteria are urgently needed.

### Treatment of Acute Heart Failure

Abnormal blood pressure, dyspnea, and hypoxemia are key medical challenges during an acute episode of HF and, as such, vasodilators, diuretics, and oxygen are key treatments. Due to its nature, diagnostic investigation of acute HF often occurs at the same time as treatment. Regular monitoring of systolic blood pressure, heart rate, heart rhythm, oxygen saturation, and urine output is recommended in patients who have not been stabilized.\(^{1,2}\)

The treatment of abnormal blood pressure depends on whether blood pressure is high or low. In hypertension, vasodilators, such as nitroglycerin and diuretics, are useful; in hypotension, vaspressors (eg, noradrenaline) or inotropes (eg, dobutamine) may be appropriate. Dopamine is an inotrope and has vasconstrictive properties when used at a high dose (5 μg/kg/min).

Intravenous diuretics and the human brain natriuretic peptide nesiritide reduce dyspnea caused by pulmonary edema. Diuretic dose appears not to affect HF symptoms or serum creatinine, but a high-dose diuretic may be more effective than a low-dose diuretic at reducing dyspnea, although this is associated with an increase in transient worsening renal function. In resistant peripheral edema, combination diuretic therapy with a loop diuretic and thiazide-like or thiazide-type diuretic may be required for a greater diuretic effect. Opiates are valuable for reducing dyspnea-induced patient anxiety and may, in addition, have a beneficial venodilatory effect. Another option in dyspneic patients is noninvasive ventilation. If breathing difficulties are
severe (eg, respiratory failure), then invasive or endotracheal intubation should be considered. Hypoxemia, which is associated with a greater risk of short-term mortality, can be alleviated with oxygen.\textsuperscript{1,2}

In HFREF patients who are not already on standard HF treatments (ie, ARBs, β-blockers, and MRAs), then these should be initiated following stabilization of acute HF. Digoxin can be given to HFREF patients with atrial fibrillation and uncontrolled ventricular rate.\textsuperscript{1} The risk of thromboembolism can be mitigated with anticoagulants, and low blood sodium levels treated with the selective, competitive vasopressin receptor 2 antagonist tolvaptan.

Several other measures are available in acute HF in addition to pharmacological management. If associated with hypervolemia, the restriction of dietary sodium to <2 g/day and fluid to <1.5 to 2.0 L/day is beneficial. Venovenous isolated ultrafiltration can also eliminate excess fluid, particularly in diuretic-resistant patients. Where mechanical circulatory support is needed, intra-aortic balloon pumps are helpful in certain types of cardiogenic shock or as a short-term solution until a ventricular assist device is implanted.\textsuperscript{1,2}

**New therapeutic strategies and targets for treating heart failure**

The latest developments in HF therapy or research cover a wide range of categories, including nonpharmacological, pharmacological, device, and cellular biology/genetics (\textit{Table I}).\textsuperscript{3,2}

**Dual angiotensin receptor and nephrilysin inhibition**

Excellent results from the PARADIGM-HF trial (Prospective comparison of ARNI with ACE inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure),\textsuperscript{62} which compared dual angiotensin receptor nephrilysin inhibition with ACE inhibition in HFREF, led to the early termination of this trial. LCZ696, a combination of the ARB valsartan and the nephrilysin inhibitor sacubitril, reduced a composite of death from cardiovascular causes or hospitalization for HF by 20% (HR, 0.80; 95% CI, 0.73–0.87; \textit{P}<0.001) in 8442 patients with HFREF vs the ACE inhibitor enalapril, a grade 1A guideline-recommended drug. All-cause mortality was reduced by 16% (HR, 0.84; 95% CI, 0.76–0.93; \textit{P}<0.001). LCZ696 was well tolerated, and unlike the combined ACE inhibitor/nephrilysin inhibitor omapatrilat, there was no significant increase in angioedema. Symptomatic hypotension was more frequently observed with LCZ696, but worsening renal function less so. This is the first time in nearly 30 years that a drug performed better than enalapril in HF in the CONSENSUS study (Cooperative North Scandinavian ENalapril SUrvival Study).\textsuperscript{63} The morbidity-mortality trial PARAGON-HF (efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in HF patients with preserved ejection fraction; NCT01920711) is ongoing to determine the effect of LCZ696 in HFPEF.

**Hormone therapy in acute heart failure**

After many years in which there have been few concrete developments in acute HF, there are good signs of progress. Serelaxin, a recombinant form of the human vasoactive hormone relaxin-2 that prevents inflammation and fibrosis, causes vasodilation, and promotes angiogenesis, relieved dyspnea and reduced cardiovascular mortality in 1161 acute HF patients in the phase 3 study RELAX-AHF\textsuperscript{64} Serelaxin was associated with a significant reduction in mortality at day 180, but not HF readmissions.

A follow-up study with a primary end point of cardiovascular mortality in 6375 acute HF patients, RELAX-AHF 2 (EudraCT No. 2013-001498-25), will help determine whether serelaxin is the first treatment to lower the risk of long-term mortality in acute HF. Other studies have shown that, in acute HF, serelaxin can reduce pulmonary capillary wedge pressure, is similarly effective in HFREF and HFPEF, and is associated with less diuretic use.

Another study, TRUE-AHF (efficacy and safety of ularitide for the TReatm ent of acU tE decom pensAted Heart Failure; NCT01661634), is investigating whether ularitide, a chemically synthesized form of the hormone urodilatin that causes diuresis by increasing blood flow in the kidney, is of value in acute HF. In preclinical studies, ularitide has been shown to have congestion-relieving and diuretic and kidney function–preserving properties.\textsuperscript{61}

**Cardiac metabolism**

Interest is reemerging in therapies that restore cardiac metabolism in HF. A recent trial in 420 patients with moderate-to-severe HF, the O-SYMBoIO trial (coenzyme Q10 as adjunctive treatment of chronic HF: a randomized, double-blind, multicenter trial with fo-
A characteristic of HF is mitochondrial dysfunction, which can be caused by decreased cardiolipin. Cardiolipin, a mitochondrial membrane lipid, maintains energy production by maintaining the proper function of the electron transport chain. A phase 2 HF study of a tetrapeptide that binds to cardiolipin and reestablishes the function of the electron transport chain, Bendavia, is currently ongoing.

**Calcium cycling**

Disruption of calcium cycling in cardiomyocytes, which is essential for cardiac contraction and relaxation, may cause HF. Contraction is caused by an increase in intracellular calcium through type 2 ryanodine receptors (RyR2), large tetrameric protein complexes. In cardiac relaxation, the sarcoplasmic-endoplasmic reticulum ATPase type 2a (SERCA2a) pumps calcium ions back into the sarcoplasmic reticulum, which induces cardiomyocyte relaxation. Restoration of disrupted RyR2 or SERCA2a could, in theory, improve cardiac contraction and relaxation and thus HF symptoms. Other potential calcium-related therapeutic targets in HF include intracellular calcium-binding proteins, such as S100A, CaMKII, and PKA.

Another approach is to sensitize cardiac myosin to calcium to improve cardiac function in HREF patients, and some progress has been made with this approach. Via increased activation of actin-myosin cross bridges, omecamtiv mecarbil increased stroke volume by prolonging the duration of systolic ejection in a phase 2 clinical trial in HREF.

**Gene therapy**

It is hoped that one day the replacement of faulty genes by undamaged, viral vector-delivered genes might correct HF defects at a molecular level. The insertion of the SERCA2a gene into isolated cardiomyocytes obtained from HREF patients led to an improvement in myocardial contractility in preclinical studies. Positive phase 1 safety results led to the CUPID trial (Calcium Upregulation by Percutaneous administration of gene therapy In cardiac Disease), a phase 2 randomized, double-blind, placebo-controlled, dose-ranging study in 39 patients with advanced HREF. Vector-delivered SERCA2a (intracoronary infusion of recombinant adeno-associated virus serotype 1) reduced the risk of prespecified recurrent cardiovascular events by 82% with high-dose treatment vs placebo after 3 years ($P=0.048$), and no safety concerns were reported. Unfortunately, in CUPID 2 (NCT01643330), the phase 2b follow-up study in 243 patients with severe HF, transgene treatment did not reduce the primary end point (recurrent HF hospitalizations and ambulatory worsening HF in the presence of terminal events, including all-cause death or transplant) vs placebo (HR, 0.93; 95% CI, 0.53-1.65; $P=0.81$) or any secondary end point. No safety issues were highlighted. Transgene dose, injection pathway, effect duration, and inadequate vector, promoter, or target were cited as potential reasons for failure.

Other gene therapy targets associated with abnormal calcium cycling that have been investigated include phospholamban (isolated failing human cardiomyocytes and sheep models) and S100A13 (isolated failing human cardiomyocytes and post–myocardial infarction porcine HF model). Additional gene therapy HF targets include β-adrenergic receptors (downregulated in HF), G protein–coupled receptor kinase 2 (GRK2, overexpressed in HF), and β-adrenergic receptor kinases.

**MicroRNAs**

MicroRNAs (miRNAs) are small noncoding RNA segments that regulate gene transcription and protein formation by silencing messenger RNA. Preclinical research into miRNAs has shown the influence these molecules have in calcium cycling, ventricular hypertrophy, and HF. Genetic knockout and the use of antagonists, chemically engineered oligonucleotide antagonists of miRNAs, have allowed the function of miRNAs to be pinpointed. miRNA25 prolongs calcium uptake in cardiomyocytes and is upregulated in HF. Injection of miRNA25 antagonist reversed HF in a mouse model. HF therapy could change the expression of miRNAs in the myocardium. Some miRNAs promote hypertrophy (miRNAs 23a, 208, and 499), while others inhibit it (miRNAs 1, 9, 98, 133, and 378). Additionally, miRNAs might make useful biomarkers.
Cell therapy

Cardiomyocytes present an interesting therapeutic solution in HF at a cellular level. HF could be improved by the implantation of stem cells into injured hearts to regenerate myocardium and improve cardiac function. Allogeneic embryonic stem cells can differentiate into cardiomyocytes, but immune suppression is required to avoid rejection, risk of teratoma increases, and ethical considerations are fundamental. Induced pluripotent stem cells can be generated from adult somatic cells using specific transcription factors, and these too can differentiate into cardiomyocytes. Ethical issues are bypassed, but the risk of teratoma remains. Research is also looking into how to program cardiac fibroblasts directly into cardiomyocytes.

Bone marrow contains different stem cells and is not hard to acquire. Secretion of growth factors, cytokines, chemokines, and the induction of new capillaries by unfractionated autologous bone marrow-derived mononuclear cells (BMMNCs) appears to account for their clinical efficacy. Results of BMMNC trials are mixed, but a large meta-analysis of 2625 patients with ischemic heart disease showed that those who received BMMNCs had a statistically higher left ventricular ejection fraction of 4.0% (95% CI, 2.90-5.02%; P<0.00001) than controls. In addition, infarct size, LV end-systolic volume, and LV end-diastolic volume were smaller for bone marrow–treated patients (all P<0.0001). The first phase 3 trial of BMMNC cell therapy in acute myocardial infarction (NCT01569178) is recruiting participants.

Unfractionated BMMNCs also contain mesenchymal stem cells, which can differentiate into cardiomyocytes in animal models. The efficacy of mesenchymal stem cells, which are hypoinmunogenic and release anti-fibrotic matrix metalloproteinases, has been observed in animal HF models. Enrichment of mesenchymal stem cells with stromal antigens leads to improved cellular regeneration and grafting. Lately, the impact on myocardial recovery of injection of allogeneic mesenchymal stem cells during implantation of left ventricular assistance devices (LVADs) was tested in 30 patients with advanced HF. Adipose tissue-derived stem cells can also differentiate into cardiomyocytes. Liposuction to obtain these cells is less invasive than bone marrow aspiration. In animal HF and myocardial infarction models, they appear to be better than BMMNCs.

The efficacy of transplanting autologous cardiac stem cells together with fibroblastic growth factors in patients with ischemic cardiomyopathy and severe HF is being investigated in the ALCADIA trial (AutoLogous human Cardiac-Derived stem cell to treat Ischemic Cardiomyopathy, NCT00981006). Another development involving cardiac stem cells is cardiospheres, a mixture of cardiac stem cells, mesenchymal stem cells, and endothelial cells that grow in self-adherent clusters. Allogeneic cardiosphere–derived cells in patients post myocardial infarction with left ventricular dysfunction are under investigation in the ALLSTAR trial (ALLogeneic heart Stem cells to Achieve myocardial Regeneration, NCT01458405), a placebo-controlled safety and efficacy trial.

The best cell type, processing method, and administration route, dose, and timing remain to be determined, but currently mesenchymal stem cells and cardiac stem cells are leading the race as the best cell candidates. Other avenues being explored with cell therapy include genetically enhancing the regenerative capacity using allogeneic cells and the transfer of genetic material into transplanted cells.

Technology in heart failure

Left ventricular assistance devices

As with other medical conditions, technological advances look set to revolutionize the realm of HF through positive, new developments in LVADs, implant-based multiparameter telemonitoring, and chronic vagal stimulation. LVADs have come a long way since they were first used to provide short-term assistance to patients in cardiogenic shock secondary to acute myocardial infarction, cardiomyopathy, or acute myocarditis. Improvements have been occurring regularly ever since, ie, miniaturization, portability, better reliability, change from pulsatile to continuous flow, and longer battery life. Totally implanted wireless LVADs could be next. This led to the use of LVADs in the medium term as a bridge to cardiac transplantation and then, following the REMATCH study (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure), to their long-term use as destination therapy in critically ill patients with advanced HF ineligible for transplantation.

The other common indications for long-term LVA are as an extended bridge to cardiac transplantation (in end-stage HF patients) and bridge to decision (in critically ill patients). In the U.S., the number of patients using LVADs over the long term is converging with the number of cardiac transplantations.
Three out of four advanced HF patients treated with an LVAD will still be alive after 2 years. It is, however, worth noting that LVADs are not risk-free; biventricular devices for right ventricular failure are associated with increased mortality rates and bleeding risk is elevated because of the requirement for constant anticoagulation. Other difficulties associated with LVAD use include infection, stroke, and thrombosis.

Treatment with LVA can lead to reverse remodeling—typified by a reduction in cardiac chamber size and myocyte hypertrophy regression—and reductions in preload and afterload. In some cases, LVAD can serve as a bridge to myocardial recovery, when a deteriorating heart stabilizes and then recuperates allowing it to circulate blood normally again. A regime of intensive pharmacological therapy can aid the process of myocardial recovery with LVAD. Device removal (explantation) and recovery is most likely to occur in a patient <50 years old, with no more than one HF event in 1 year caused by idiopathic dilated cardiomyopathy or myocarditis rather than ischemic cardiomyopathy. It has, however, been speculated that the addition of revascularization to pharmacotherapy and LVAD could lead to myocardial recovery in patients with ischemic cardiomyopathy in nonadvanced HF without irreversible myocardial damage. Adjunctive cell-based therapy may also have a role to play here. The prospect of myocardial recovery with LVA may signal the beginning of a change in our perception of advanced HF as irreversible.

**Implant-based multiparameter telemonitoring**

Implant-based multiparameter telemonitoring is a promising new technology to improve outcomes in HFREF. In a recent randomized clinical trial of telemonitoring in 664 HFREF patients with a recently implanted ICD or CRT-D, the primary composite outcome (clinical score combining all-cause death, overnight HF hospital admission, change in NYHA class, and change in patient global self-assessment) worsened less in the telemonitoring group than the control group after 1 year (18.9% vs 27.2%; OR, 0.63; 95% CI, 0.43–0.90, \( P=0.013 \)). With appropriate data-management protocols in place, telemonitoring provides a potential means of further reducing outcomes in HFREF patients implanted with an ICD or CRT-D. As not all previous study results have indicated this, consistent reporting of the benefits of remote monitoring is required before this technology becomes more widely accepted.

**Chronic vagal stimulation**

Direct vagal nerve stimulation could be used to enhance parasympathetic tone in HF, but it is still too early to conclusively say how useful this technique will be in HF. Quality of life measures were significantly improved by vagal nerve stimulation after 6 months vs control in the NECTAR-HF trial (NEural Cardiac Therapy for Heart Failure), but the primary end point of change in left ventricular end systolic diameter was not (−0.04±0.25 cm vs −0.08±0.32 cm for stimulation vs control). More information is expected from forthcoming studies in the next few years.

**CONCLUSION**

HF is a disease of our times: as populations in developed nations age, chronic HF and HFPEF in particular will become more prevalent, putting further strain on current healthcare systems in terms of increased morbidity, mortality, and costs. Nevertheless, thanks to advances in HF therapy and management, the prognosis of patients with HF is better than it once was. Our understanding of HF has never been so good, but as always there is room for improvement. A better understanding of the pathophysiology of HFPEF and of ways of recognizing HFPEF phenotypes will be particularly useful for finding ways other than antihypertensive therapy to manage and treat HFPEF.

Progress has also been made in the areas of HFREF and acute HF. Heart rate has been identified as a prognostic factor in HFREF, and ivabradine has provided a new way of reducing HFREF outcomes further. The angiotensin receptor–neprilysin inhibitor valsartan/sacubitril also promises to further improve outcomes in HFREF.

A lot of research is going into the impact of comorbidities on HF and into new ways of treating these. Research is also looking into novel ways of treating HF, such as by targeting cardiac metabolism or calcium cycling. A modern-day technological revolution has allowed us to envisage replacing cardiomyocytes using gene therapy, miRNA, and cell therapy. This revolution is not only biological and genetic, but electronic too. Advances in LVAD technology have allowed us to begin dreaming of myocardial recovery as a realistic treatment objective in advanced HF. The future of HF treatment and management is full of possibilities, and innovation is the watchword.

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Understanding and Treating Heart Failure

Expert Answers to Three Key Questions

1. What is the role of the heart failure nurse?
   
   J. P. Riley

2. What is the role of telemonitoring in heart failure?
   
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3. Gene therapy for heart failure: the end of the beginning?
   
   A. C. Morley-Smith, C. Hayward, S. E. Harding, A. R. Lyon
What is the role of the heart failure nurse?

Jillian P. Riley, PhD, RN, NFESC
National Heart & Lung Institute - Imperial College - London - UK

The specialized role of the heart failure nurse rose to prominence during the 1990s. Studies reported benefits in outcomes in patients receiving follow-up care by a multidisciplinary care team and in which nurses were key players. Since then, the nurse’s contribution throughout the journey of the heart failure patient has become widely recognized. In many countries, heart failure nurses are now establishing their role in optimizing outcomes during admission for acute heart failure, routine follow-up and monitoring, and at the end of life. Recent interest in service development for the prevention of heart failure opens up newer avenues for nurses. This paper considers the contribution of the nurse to an effective heart failure service and discusses the value of a “task sharing” approach to care.

Heart failure continues to increase in prevalence and now affects millions of people throughout the world. Despite enormous advances, those affected remain at an increased risk of a reduced quality of life. Patients have repeated hospital admissions and many die prematurely. The developing evidence base for medications and implantable devices has contributed to an improvement in outcomes. However, these technological advances carry an increased risk of adverse events and increase the “burden” of self-care. In addition, there is a growing population of elderly and frail patients with comorbid conditions.

This all adds to the complexity of patient management. In many countries, this has led people to reconsider both the way in which heart failure services are organized and the delivery of structured outpatient monitoring and follow-up. The boundaries of traditional and professional health care roles are changing and heart failure nurses now provide a range of health care services.

Nurses’ roles and responsibilities differ throughout Europe. This variation largely relates to the legislative framework within which health care professionals work. However, it is likely that local “customs and practices” have also defined the roles of members of the heart failure team. This paper acknowledges these wide variations and role diversities. Yet, it also acknowledges that the role of the nurse within the heart failure team can transform the patient’s experience through a focus that goes beyond the biomedical approach and considers the psychological and social influences on illness and outcome. Starting with a discussion of the traditional role for the nurse in the management of chronic heart failure disease, this paper discusses some of the newer areas where the heart failure nurse is establishing a role, eg, monitoring during an acute inpatient episode, preventing heart failure, and managing care at the end of life (Table I). The paper concludes by describing the education and support necessary to strengthen this role development.

Keywords: acute heart failure; disease management; heart failure; nurse-led care; patient education

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Table I. Roles and responsibilities of heart failure nurses.

| Alleviate distressing symptoms (physical and emotional) |
| Optimize evidence-based heart failure management (medication and self-care support) |
| Monitor and recognize effectiveness of treatment |
| Triage to safe environment for care |
| Provide patients and their family with information, education, and support |
| Ensure prompt communication between the patient/family and the health care professional |
| Provide end-of-life care |

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HEART FAILURE
disease management programs

Organization of care

Emphasis for the majority of work in the management of chronic disease has been on the organization of care to ensure a “seamless service” between hospital and home and help the patient live with their illness. Early studies on approaches to the management of heart failure led the way for this reorganization of care, allowing nurses to quickly establish a position within heart failure management programs to monitor for clinical deterioration, optimize medication, and provide education and support for self-care. These early studies demonstrated the effectiveness of heart failure management programs, and these results have been confirmed through a meta-analysis that reported a reduction in the risk of hospital readmission for heart failure (risk ratio [RR], 0.74; 95% CI, 0.63-0.87), all-cause hospital admission (RR, 0.81; 95% CI, 0.71-0.92), and mortality (RR, 0.75; 95% CI, 0.59-0.96) in patients who received structured follow-up by a specialized heart failure team. Within these programs, nurses primarily managed patient care through regular follow-up visits in either a heart failure clinic or at the patient’s home.

Various follow-up models now exist. These include face-to-face and remote approaches. Local need and expertise will influence the way in which individual services are organized. However, patients are likely to benefit from different approaches at varying time points in their disease trajectory. For example, home visits may be particularly useful soon after hospital discharge for the elderly or for those with functional limitations that make traveling to the hospital or clinic problematic. Home visits may be time consuming for health care professionals, especially regarding travel time; therefore, this may limit the number of patients who are able to receive this level of care. Remote monitoring and follow-up using telephone contact or a specialized telemonitoring program may provide a suitable alternative.

A Cochrane meta-analysis of randomized studies of remote monitoring in patients at a high risk of rehospitalization reports a reduction in the risk of heart failure–related hospital admission with both telephone follow-up and telemonitoring (telephone [RR, 0.77; 95% CI, 0.68-0.87, P<0.0001] and telemonitoring [RR, 0.79; 95% CI, 0.67-0.94, P<0.008]). A significant reduction in all-cause mortality was observed with telemonitoring (RR, 0.66; 95% CI, 0.54-0.81, P<0.0001), whereas there was a nonsignificant reduction using telephone follow-up support (RR, 0.88; 95% CI, 0.76-1.01, P=0.08). These findings have been challenged by two recent and large studies. The first study was conducted in a stable, lower-risk patient group, where telemonitoring data were reviewed and responded to by physicians in a telemonitoring call center, and the second study was a telephone-based interactive system, where almost 50% of the sample did not use the equipment for the entire study. Remote monitoring has a useful role in widening access to care, which may be particularly valuable to patients living in remote areas. The substantial increase in patients with heart failure that is predicted for the next decade shows that the development of sustainable services for follow-up is needed, something that may be aided by remote monitoring. In many remote monitoring services, nurses play a central role in regularly reviewing the data, triaging patients for early follow-up through a home visit or outpatient review, answering patient or family queries, and helping the patient develop self-care skills.

Although patients are likely to benefit from contact with a heart failure team soon after discharge from the hospital (preferably within 10 days), the follow-up frequency should be tailored to an individual’s needs. The physician can use this appointment to assess the patient and discuss current and future treatment options and prognosis with the patient. The heart failure nurse can reinforce information on heart failure management, answer patient and family questions, identify and manage early anxieties, and help the patient develop self-care skills. However, outlining professional responsibilities in this way is artificial and an effective heart failure team will ideally work together to ensure that all goals of the first outpatient review are addressed.

The level of care that is offered in multiprofessional disease management programs is now recognized in international guidelines. Extending this, and acknowledging the
What is the role of the heart failure nurse? - Riley

What is the role of the heart failure nurse within the team, the Heart Failure Association of the European Society of Cardiology has suggested that each acute hospital have 1 heart failure nurse for every 100 000 people. Disease management programs are now established in many European countries. A recent survey of 33 countries of the European Society of Cardiology reports that heart failure clinics are present in 25 countries (75%). Encouragingly, this represents an increase from an earlier survey.

However, there are variations in the structure of these clinics and the heart failure nurse is involved in only 18 of the 25 countries with heart failure clinics (72%). These data are limited by their method of data collection, but suggest that many patients may still not be able to access high-quality heart failure care provided by a multidisciplinary team.

**MONITORING**

Monitoring is a key component of heart failure management programs. International guidelines have yet to provide recommendations on key monitoring parameters, something that may be related to the limited evidence on the topic. Despite this, it appears intuitive to regularly monitor heart failure symptoms, fluid volume status, hemodynamic values, laboratory blood tests, and self-care understanding (Table II). Local guidelines may provide some clarity (eg. in England, monitoring is recommended at intervals of 6 and 12 months for stable patients). More frequent monitoring will be necessary during periods of therapy optimization, immediately following hospital admission for worsening heart failure, or during periods of deteriorating symptoms. The specialist heart failure nurse’s focus is on the routine monitoring of stable patients, checking for side effects of medication during periods of optimization, and reviewing barriers to self-care.

**Medication**

The evidence for heart failure medication is strong. Many of these drugs are started at low doses and then steadily increased, which requires careful patient monitoring for both drug and adverse effects. Patients do not necessarily achieve the target dose quickly and some never do. A multidisciplinary team approach may help. For many years, nurses have worked within clinical protocols to optimize medication. Such protocols outline good practice advice for the management of common heart failure medications, guide the nurse on when to measure blood chemistry, and outline the changes in blood chemistry and vital signs that necessitate referral to a physician and those values that are considered safe for uptitration.

Within the UK, the nurse’s contribution to optimal medication has been extended further. In 2006, changes in the law enabled independent nonmedical prescribing. Following a period of additional education and mentoring, nurses can independently prescribe medication, and therefore, play a more autonomous role within the heart failure management team. This process has gained acceptance among professionals and patients and has been positively evaluated for providing safe and timely care. A documented evaluation of nurse prescribing has confirmed that nurses appropriately prescribe medications. Patients were satisfied with nurse prescribing and reported no difference between nurse prescribers and physicians in the quality of care, the information they received, or support for self-care. Although the results from a more robust evaluation are still awaited, such studies point to the safety and quality of care that can be provided by widening the “pool” of health care professionals, with the responsibility of safely prescribing medications.

**Self-care support**

If indicators of worsening heart failure are recognized and managed early, it may be possible to prevent some hospital admissions. Self-care requires patients to monitor their condition, recognize significant changes, and take appropriate actions. Breathlessness commonly triggers patients to seek professional help. However, delays in presenting to a health care professional can be lengthy with patients only seeking professional help when their

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**Table II. Key monitoring undertaken by heart failure nurses during follow-up.**

<table>
<thead>
<tr>
<th>Clinical assessment</th>
<th>Signs and symptoms</th>
<th>Functional capacity</th>
<th>Fluid status</th>
<th>Cardiac rhythm</th>
<th>Cognitive status</th>
<th>Nutritional status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of medication</td>
<td>Dose</td>
<td>Side effects</td>
<td>Medication recall</td>
<td></td>
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<tr>
<td>Laboratory tests</td>
<td>Urea and electrolytes</td>
<td>Creatinine</td>
<td>Hemoglobin</td>
<td></td>
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<tr>
<td>Self-care ability</td>
<td>Knowledge</td>
<td>Barriers to self-care</td>
<td>Anxiety and depression</td>
<td>Cognitive function</td>
<td></td>
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</tr>
<tr>
<td>Devices</td>
<td>Patient understanding</td>
<td>Symptoms</td>
<td>Adverse events</td>
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</table>
symptoms become intolerable. Various reasons for such delays have been described with studies reporting difficulty accessing healthcare, limited self-care information, and uncertainty over when to seek professional help. Other important aspects of self-care behavior include lifestyle behaviors and adherence to medication, yet adherence is an acknowledged problem. Again, there are probably several explanations, including social and economic reasons that leave prescriptions unfilled. Patients may have limited knowledge or may simply forget, and some patients will deliberately decide not to take their medication due to their concerns about both the drug and side effects. Wide variation in patients’ adherence with lifestyle advice and self-care behaviors is not surprising. For example, in 2007, the EuroHeart Failure Survey reported that patients recalled only 46% of the self-care advice that they had received. In a substudy of the COMET trial (Carvedilol Or Metoprolol European Trial), Ekman et al reported that adherence with medication was associated with patient beliefs about their medication. This all points to the complexity of education for self-care and supporting self-care behavioral changes (Table III). Successful education depends on the extent to which the patient establishes rapport with and trust in the advice. For the professional, time is needed to establish individual needs, assess the patient’s perspectives and beliefs, and provide appropriately tailored information.

This is time consuming and it is rarely possible to achieve within the time constraints of a routine physician outpatient clinic. Within heart failure management programs, the heart failure nurse has embraced the role of providing patient education and supporting the develop-

### Table III. Key issues in self-care support and specific nursing actions.

<table>
<thead>
<tr>
<th>Education topic</th>
<th>Nursing actions</th>
</tr>
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</table>
| Definition, etiology, and trajectory            | • Provide oral and written information tailored to individual education grade, health literacy, and culture/language  
• Use pictorial health diaries when necessary  
• Provide information at regular time intervals. |
| Symptom monitoring and self-care                | • Provide information to support self-care  
➢ In the case of increasing dyspnea or edema or a sudden unexpected weight gain of >2 kg in 3 days, increase the diuretic dose and/or alert the patient’s health care team. |
| Medication                                      | • Provide written information on dosing, effects, and side effects  
• Encourage regular recording of weight and blood pressure  
• Provide an individualized medication “passport”. |
| Diet and alcohol                                | • Individualize information on fluid intake to be consistent with body weight, climate, etc  
• Individually tailor alcohol advice to the etiology of heart failure, eg, abstinence for alcoholic cardiomyopathy. |
| Smoking and recreational drugs                  | • Offer cognitive behavioral theory (if trained) and psychological support  
• Refer for specialist advice for smoking cessation, drug withdrawal, and replacement therapy. |
| Exercise                                        | • Encourage exercise within physical limitations  
• Provide advice on methods of exercise, such as a specific heart failure exercise program. |
| Immunization                                    | • Communicate information on local guidance and immunization practice  
• Discuss timing of diuretics, environment for sleep, etc. |
| Sleep and breathing                             | • In the presence of sleep disordered breathing, encourage weight reduction/control and use of mask support therapy, if appropriate. |
| Psychosocial aspects                            | • Communicate information on disease, treatment options, and self-care  
• Refer to specialist for psychological support, when necessary. |
ment of self-care skills. Many nurses now run clinics that focus on patient education. Group education sessions and patient support groups may also be beneficial. Technology can provide supportive self-care resources. For example, some telemonitoring systems provide information videos and reminders. Internet-based information sites also exist, eg, heartfailure matters.org.22 However, the greatest benefit will probably be seen when the advice from technological resources is integrated into routine clinical visits and telephone reviews and reinforced at regular intervals. We have reported that such an approach can increase the patient’s ability to provide self-care.5

Self-care support extends beyond providing information to identifying and addressing barriers to self-care, such as anxiety, depression, cognitive impairment, and low levels of education and health literacy.

ACUTE HEART FAILURE

The focus for the role of the heart failure nurse has been on outpatient follow-up. Yet, many patients are admitted with acute heart failure as either the first manifestation of heart failure or an acute decompensation of chronic heart failure. During the acute phase, the immediate focus is on alleviating distressing symptoms (both physical and emotional). However, once stabilized, the patient should be triaged to an appropriate environment for continued monitoring of the patient’s mental status, respiratory rate, fluid balance, and hemodynamic stability. The heart failure nurse then coordinates care, provides heart failure education, and ensures referral to the heart failure team for postdischarge follow-up.23

Outcomes are improved when care is provided by a specialized heart failure team and by ward nurses familiar with the management of heart failure. A recent UK audit reported lower in-hospital mortality when patient care was managed in specialist cardiology wards (7.8%) vs general medical wards (13.2%). This reduction in the risk of death extends into the follow-up period, suggesting a longer-term benefit from ensuring that patients start an appropriate heart failure pathway as early as possible. Mortality was lower for patients referred for follow-up, a specialist heart failure nurse can provide an outreach service. Using medical admission records, they can identify patients with suspected heart failure, act as a point of contact for specialist advice, and ensure appropriate discharge planning and follow-up.

PREVENTION OF HEART FAILURE

The individual etiology of heart failure varies; however, certain populations have a high incidence of heart failure (eg, following myocardial infarction or in patients with hypertension). While the nurse has established a clear role in the primary and secondary prevention of coronary heart disease, the heart failure pathway after a myocardial infarction has received less attention and many patients receive little or no

Figure 1. Postdischarge survival rates for patients referred to heart failure nurse follow-up on hospital discharge.

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The nurses’ role in heart failure prevention clinics has emphasized the individual patient’s risk status and has encouraged adherence to medication and healthy lifestyle behaviors. This could be extended to monitoring for potential side effects of medications, optimizing doses, and commencing appropriate medication. Critics of these studies may point to difficulties replicating these complex study interventions in routine practice. However, similarly complex nurse-led interventions were used in the EuroAction trials and effectively implemented for the secondary prevention of cardiovascular disease. Questions remain about patients’ willingness to be involved in regular follow-up in the absence of overt disease, in what may be perceived as the “medicalization” of daily life. Should larger studies of chronic heart failure prevention programs extend these early findings and demonstrate clear evidence of benefit, such challenges will need to be addressed.

Other “at risk” populations are similarly being targeted for prevention and early detection of heart failure. The field of cardio-oncology is one such example. Survivorship from cancer is increasing and many patients now live for many years after treatment with potentially cardiotoxic chemotherapeutic agents and they remain at an increased risk of developing heart failure. Regular echocardiography may enable earlier detection of heart failure and appropriate treatment. This subgroup of heart failure patients may have different information and support needs and may benefit from specific psychosocial support. The role of the nurse in meeting patient’s needs in this area is currently underresearched.

END-OF-LIFE CARE

The progressive nature and high mortality of heart failure necessitates a role for optimizing care toward the end of life. The aim of palliative care is to provide holistic care that embraces the management of symptoms and offers psychological and spiritual support. Predicting prognosis in heart failure is not always easy, as the patient’s pathway is rarely linear. Rather it encompasses periods of health punctuated by periods of poorer physical functioning. Identifying when to move to an end-of-life pathway is not easy. Consequently, such difficult, yet important, topics may be left unsaid.

Ideally, all professionals in the heart failure team should provide palliative care and seek advice and support from specialist palliative care services when necessary. Heart failure specialist nurses are well placed to address patient concerns and make appropriate referrals to both health and social care services. The evidence to support the local implementation of palliative care services, particularly the role of the nurse, is limited. Various examples of palliative care services in heart failure have been described. Many use a shared care approach between cardiologist and specialist palliative care physicians. Within these models, the heart failure nurse is a key worker that liaises between primary, secondary, and hospice care. Using data collected from two integrated heart failure and palliative care services in the UK, Johnson et al suggest that end-of-life care planning, referral to specialist palliative care services, and enabling patients to die in their preferred place was mostly achieved by the actions of the heart failure nurse who discussed patients’ concerns and was central to the coordination of their care.
CONCLUSION

Significant progress has been made to improve the outcomes for patients living with heart failure and patients can now expect to live for several years. Despite this, there is still much that can be done. Newer therapies that promise reductions in symptoms and improvements in health-related quality of life are in the pipeline. In addition, much can still be done to streamline the care provided to ensure that patients do not “fall in the gap” between hospital and home and between active follow-up and end of life. All patients should also expect to receive the same high standard of care regardless of age or sex. Similar challenges are faced by all health care organizations—to provide high-quality care despite the increasing number of people with heart failure, the increasing complexity of the disease, decreasing professional resources, and increasing patient expectations for care. Imaginative solutions will be required. Optimizing the contribution of all members of the heart failure team, including the heart failure nurse, will go some way toward this goal.

EDUCATION FOR ROLE EXPANSION

Such roles must be underpinned with appropriate education. Nurses require sufficient education to support safe practices. Patients deserve to be cared for by knowledgeable professionals in whom they can place their trust. Nurse education varies between countries, but to provide some standardization, the European heart failure nurse’s curriculum has been updated. However, access to specific education and training for heart failure nurses is variable. For nurse education, it is the responsibility of country-specific registrations to regulate for safe care, yet it is the specialist professional organizations that can help develop roles and expand professional horizons to improve the standards of care.

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What is the role of the heart failure nurse? - Riley


Heart failure disease management programs are well established and their role in supporting self-care and improving outcomes is recognized in international guidelines. However, access to such programs is limited. Telemonitoring, the monitoring of patients using information technology to collect health-related information and transmit this data to a health care professional, who is remote from that patient, offers the opportunity for the patient and health care professional to adopt a proactive approach to the early detection of clinical deterioration, optimization of medication, and education for self-care. However, the evidence that it improves outcomes over and above the best usual practice is thin, meaning that any benefit will come at an additional expense and organizational disruption. Convenience and acceptability are high for the patients, but adoption remains slow due to a frequent lack of reimbursement.

Heart failure typically affects the elderly, and their limited mobility and lack of social support may make frequent attendance at the hospital, clinic, or doctor’s office difficult. In some countries, home visits by a doctor or nurse specialist are possible, but are costly in travel time for the health care professional.

Therefore, traditional health care approaches often struggle to meet the demands of evidence-based care for heart failure. This problem is set to increase as the population ages at an unprecedented rate. The percentage of European citizens who are 65 and over is expected to increase from 17% to 30% between 2010 and 2060.4

### SELECTED ABBREVIATIONS AND ACROYSMS

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>ACRONYM</th>
<th>DESCRIPTION</th>
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<tr>
<td>CRT</td>
<td>Cardiac resynchronization therapy</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<th>ACRONYM</th>
<th>DESCRIPTION</th>
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<tr>
<td>CHAMPION</td>
<td>CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA class III heart failure patients [study]</td>
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<tr>
<td>COMPASS-HF</td>
<td>Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure [study]</td>
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<tr>
<td>CONNECT</td>
<td>Clinical evaluation Of remote Notification to rEduCe Time to clinical decision [study]</td>
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<td>DOT-HF</td>
<td>Diagnostic Outcome Trial in Heart Failure</td>
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<td>HOME-HF</td>
<td>HOME Heart Failure [study]</td>
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<td>IN-TIME</td>
<td>INfluence of home moniToring on mortality and morbidity in heart failure patients with IMPaired LEft ventricular function [study]</td>
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<td>REM-HF</td>
<td>RE mote Monitoring: an evaluation of implantable devices for the management of the Heart Failure patients [study]</td>
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<td>TEN-HMS</td>
<td>Trans-European Network–Home-care Management System [study]</td>
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<td>TIM-HF II</td>
<td>Telemedical Interventional Management in Heart Failure II [study]</td>
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<tr>
<td>WHARF</td>
<td>Weight monitoring in HeART Failure [study]</td>
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**Keywords:** e-health; heart failure; remote monitoring; telemonitoring

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In response to the ever increasing demand and the challenge of funding, policy makers have promoted the use of “e-health” (i.e., the use of information and communication technologies to support health and health-related activities) as a means to improve outcomes and ensure the sustainability of health care provisions. The belief is that this will widen access to high-quality care and support care closer to home—technology is seen as a tool that can help take the expertise to the patient, rather than the patient to the expertise.

In theory, technological innovation should improve interprofessional cooperation, information sharing, decision support, and flexibility in the health care system. However, the impact of such innovation is reduced by legal, ethical, and data protection concerns. Health care professionals may be resistant to such innovations, particularly if the technologies are considered “solutions seeking a problem” and where the evidence for the impact on quality of care is seen as less than robust. Ensuring proper integration of new technologies into the health care system is often difficult, requiring process redesign or “disruption.”

Regulatory bodies and reimbursement authorities find it difficult to react quickly, or consistently, to this rapidly changing area, thus creating further barriers to implementation.

**WHAT IS TELEMONITORING?**

Telemonitoring can be defined as the monitoring of patients using information technology to collect health-related information and transmit it to a remotely located health care professional. Telephone support could be considered the simplest form of telemonitoring, but more typically, telemonitoring is taken to mean the use of equipment (e.g., a sphygmomanometer or weighing scale) at the patient’s home to collect data, which is then transmitted over the telephone or via the internet to a health care professional. Data from devices implanted for therapeutic reasons, such as a pacemaker or defibrillator, can also be remotely monitored. Implantable devices that are solely used for monitoring purposes have recently been developed and these devices will be discussed in this article.

**RATIONALE FOR TELEMONITORING**

Patients with chronic heart failure are prone to frequent exacerbations, with worsening symptoms that reduce their quality of life and substantially increase their use of health care resources. Despite many advances in therapy, the readmission rate remains high—typically around 25% within 30 days. Management is not straightforward and requires both specialized knowledge to optimize care and frequent monitoring to ensure stability.

Education of the patient regarding the nature of the chronic condition, the need for therapy, the symptoms that may indicate possible decompensation, and methods for self-care are viewed as central to a good heart failure management program.

Retrospective studies suggest that a patient typically notices a change in their symptoms several days before seeking help. Physiological variables may start to change many days before a patient notices any change in symptoms. The premise for telemonitoring is that frequent monitoring by a health care professional may enable earlier intervention to treat deterioration.

**WHAT CAN BE MONITORED?**

Traditionally, patients are taught to monitor weight and symptoms or signs of fluid overload. These measurements can easily be made remotely, along with blood pressure and heart rate. Questions commonly asked during patient assessment can be included in specific telemonitoring systems. For example, the patient can answer using a “yes/no” response button to questions, such as “did you sleep with extra pillows last night?”

In studies that have reported the actions taken by health care professionals as a result of telemonitoring data, some have shown that the most frequent action relates to volume overload presenting as dyspnea or weight gain. It seems appropriate to consider monitoring weight and key disease-related symptoms as the minimum data set for a telemonitoring service.

For implanted electrical devices, such as pacemakers or defibrillators, it is possible to monitor the tech-
nical features of the device and episodes of arrhythmia (such as atrial fibrillation or ventricular tachycardia/fibrillation), the therapeutic actions of the cardioverter-defibrillator (such as antitachycardia pacing or a direct current shock), and a range of physiological variables, often termed “heart failure diagnostics.” Such “diagnostics” include intrathoracic impedance, which can be measured between the right ventricular lead and the generator of a pacing device. Accumulating intrathoracic fluid decreases impedance, which identifies trends that would suggest the development of pulmonary edema. Other physiological measurements that can be remotely monitored with such devices include heart rate variability, nocturnal heart rate, and patient activity.

Data from implanted devices can also be linked to data from stand-alone devices, such as a sphygmomanometer or weighing scales, and this data can provide an even broader assessment of the patient’s cardiovascular status (Figure 1). It is possible to identify patients at a much higher risk of decompensation by applying an algorithm to the trends observed for a number of remotely monitored variables in cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator systems. “High”-risk individuals that have a 10-fold increased risk of decompensation in the next month compared with “low”-risk individuals can be identified, although the absolute risk remains low (≈7%). Therefore, it is important that the health care professional responsible for monitoring the data does not overreact, as this could lead to increased clinical activity (such as clinical review or hospitalization) without necessarily improving outcomes. Just such an effect was observed in the DOT-HF study (Diagnostic Outcome Trial in Heart Failure), a randomized study where clinicians and patients were issued with an “alert” in response to changes in only one physiological parameter—intrathoracic impedance. There was no change in mortality in this study, but there was a 79% increase in the risk of being hospitalized with suspected decompensation ($P=0.02$).

**DATA TRANSMISSION**

The privacy and security of personal data are of concern to patients, health care professionals, and health care regulators. It is important that the monitoring data be encrypted before being transferred through the home telephone line, mobile phone, or internet. Access to any telemonitoring “station” should also be secure, with access restricted to people with a legitimate interest in the data and the patient’s management. Web-based applications can easily be password protected, but concerns regarding the storage of data on servers in countries with less stringent data protection rules than in the European Union can cause problems.
TRIAGE OF REMOTELY COLLECTED DATA

Remotely transmitted data are typically compared against preset “limits,” which are often tailored to the patient’s physiology. Customarily, the initial response to data that possibly represents clinical deterioration, such as an increase in weight or symptoms, is a telephone assessment and/or advice from a trained heart failure professional, often a specialist nurse. Early review or a planned hospital admission is necessary only when the issues cannot be resolved remotely through telephone advice on medication or lifestyle. In some countries, the initial triage of data occurs at a call center, with the patient’s usual health care provider contacted only if required.

In the HOME-HF study (HOME Heart Failure), a randomized trial of home telemonitoring in West London, UK, only 64% of the telemonitored patients had data-triggered contact that required action in the 6-month period after discharge from the hospital. This was an average of one phone call to a patient each month during the first 3 months of monitoring. After telephone contact, only 19% of patients required early clinical review in secondary care. Similarly, in the IN-TIME study (INfluence of home monitoring on mortality and morbidity in heart failure patients with IMpaired Ieft ventricular function) on remote monitoring of implanted devices, which remotely followed-up 333 patients over 12 months, the telemonitoring center sent information on 280 patients to the individual centers, with 238 patients being contacted at least once. In more than 60% of the cases, this was only because there had been a gap in daily transmission of data for more than 3 days. For 75% of patients, there were ≤3 telephone contacts per year. Timeliness of response to remotely collected data is important for both technical and legal reasons. A standard operating procedure should be set up before a service is introduced; patients need to be aware of how often their data will be viewed and what to do when feeling unwell. In some systems, the patients can contact their health care professional or a call center at any time of the day or night, but in most services, such contact is limited to working hours, and access to other health care services should continue as usual. Delays in responding to changes in monitored data defeat the purpose of remote monitoring, and health care staff involved in telemonitoring need to be empowered to make decisions and receive guidance as to when to contact the cardiologist, implanting physician, etc.

WHAT IS THE CLINICAL BENEFIT OF TELEMONITORING?

Despite increasing interest in telemonitoring in heart failure and a growing number of service providers, there is no clear guidance in international heart failure guidelines as to whether telemonitoring is worthwhile, and if so, for which patients and at what time point it is valuable. Therefore, further research is recommended. Early studies of telemonitoring were observational, with before and after comparisons potentially inflating the estimates of clinical effectiveness. More recently, several randomized trials have been conducted in a variety of health care settings.

NONIMPLANTED SYSTEMS

One of the first, large randomized trials to assess the regular use of telemonitoring rather than telephone monitoring was the WHARF study (Weight monitoring in HeArt Failure), which enrolled 280 patients hospitalized with New York Heart Association (NYHA) class III or IV and an ejection fraction less than 35%. Patients were randomly assigned to receive usual care or usual care plus daily telemonitoring of weight and symptoms. Patients were followed-up for a maximum of 180 days. The study reported no difference in the primary end point of all-cause rehospitalization during 6 months of monitoring (65 [47%] in the telemonitoring group vs 67 [47%] in the usual care group, P=0.28) and no difference in the time to rehospitalization or death (P=0.16). They did, however, report a 56% (P=0.003) reduction in the mortality rate in the telemonitoring group.

The TEN-HMS study (Trans-European Network–Home-care Management System) randomized 426 patients (mean age 67 years) with NYHA class II to IV and left ventricular systolic dysfunction (left ventricular ejection fraction <40%) to home telemonitoring, nurse telephone support, or usual care. This multicenter study recruited patients from 16 centers and 3 European countries. There were no statistically significant effects on heart failure–related hospitalization or average length of stay for such admissions. Although it was not a primary outcome, there was a statistically significant reduction in mortality in the telemonitoring group compared with the usual care group at 1 year (P=0.03). A greater number of patients in the telemonitored group were ultimately on optimal drug therapy vs the usual care group.

The HOME-HF study, a randomized trial of home telemonitoring in a typical elderly heart failure population (mean age, 71; 45% were >75 years), which included those with
either preserved or impaired left ventricular systolic function, compared 6 months of daily telemonitoring with specialist heart failure care in 182 patients discharged from 3 district hospitals in West London, UK. There was no difference in the primary outcome of all-cause hospitalization, but a significant decrease in the proportion of emergency hospitalizations for heart failure (usual care [81%] vs telemonitoring [36%], \( P=0.01 \)). There was also a reduction in the number of visits to the emergency room and secondary care clinical visits with telemonitoring.

A recent meta-analysis of randomized trials, which included 6317 patients, suggested that telemonitoring was associated with a non-significant 24% reduction in mortality for office hour-based programs (95% credible interval, 51% reduction to 18% increase) and a non-significant 51% reduction in mortality for programs that provided medical support 24 hours per day, 7 days per week (95% credible interval, 80% reduction to 18% increase). Excluding the HOME-HF study (with only 180 patients) from the meta-analysis, where support to the usual care group may have been better than “usual” care, made these estimates statistically significant, showing that the estimates are perhaps rather unstable.

Most of the recently published small, randomized trials have been conducted on patients who have had a recent episode of decompensation. Koehler et al studied a group of 710 German patients receiving optimal medical therapy with stable, ambulatory heart failure with NYHA class II or III and an ejection fraction <35%. Patients were randomized to usual care or daily telemonitoring, where data on weight, blood pressure, and a three-lead ECG were transmitted. The authors reported reasonable compliance with remote monitoring, with 70% of patients in the remote monitoring arm transmitting data daily. There were no statistically significant differences in the rates of all-cause mortality (hazard ratio \( HR, 0.95 \), 95% CI, 0.67-1.17, \( P=0.87 \)), cardiovascular death (HR, 0.86, 95% CI, 0.56-1.31, \( P=0.49 \)), or hospitalization between the two groups. Patients in the remote monitoring arm showed a significant improvement in physical functioning, which was measured using the short form 36 (SF-36) questionnaire (\( P<0.05 \)). In this study, >90% of the patients were taking angiotensin-converting enzyme inhibitors and \( \beta \)-blockers at baseline and had heart failure for >6 years on average, perhaps limiting the scope for the addition of telemonitoring.

An additional larger study is currently underway in Germany that is targeting higher-risk patients (TIM-HF II study [Telemedical Interventional Management in Heart Failure II]; NCT01878630). An additional larger study is currently underway in Germany that is targeting higher-risk patients (TIM-HF II study [Telemedical Interventional Management in Heart Failure II]; NCT01878630).

**IMPLANTED SYSTEMS**

Observational data from a large US registry suggests that patients who are remotely monitored have a lower risk of mortality or hospitalization than patients who are not remotely monitored, although selection bias is highly likely in terms of both patients choosing to be remotely monitored and physicians willing to offer this service. Remote transmissions occurred weekly on average, with additional clinical visits occurring twice per year on average.

In the CONNECT study (Clinical evaluation Of remote NotificatioN to rEduCe Time to clinical decision), automatic clinician alerts were programmed for serious clinical “events,” such as two implantable cardioverter defibrillator shocks, ventricular rate >120 beats/minute in atrial fibrillation, or atrial fibrillation episodes lasting more than 12 hours per day. There was evidence for a reduced length of stay for cardiovascular hospitalizations, and the average time from clinical event to clinical decision was reduced from 22 days in the usual care arm to 4.6 days in the remotely monitored arm (\( P<0.001 \)).

In the DOT-HF study, heart failure hospitalization increased by 79% after programing an “alert” in response to a preset change in trans-thoracic impedance.

In the IN-TIME study, 664 patients were randomized (1:1) to automatic daily implant-based multiparametric telemonitoring in addition to usual care or usual care alone at 36 centers in Australia, Europe, and Israel. At 12 months, 19% of patients in the telemonitoring arm had a worsened composite score compared with 27% in the usual care arm (\( P=0.013 \)). Although mortality was not the primary end point, 10 patients died in the telemonitoring arm compared with 27 in the usual care arm (\( P=0.004 \)). Most of the actions were related to checking on compliance with the monitoring, reduction in CRT efficacy (CRT pacing <80%), or identification of atrial arrhythmias.

Within 12 months, the REM-HF study (REmote Monitoring: an evaluation of implantable devices for the management of Heart Failure patients), one of the world’s largest randomized trials of remote monitoring of implanted devices, will report the results after monitoring 1650 patients who were randomized to either weekly remote data downloads or usual care at 9 English hospitals, with a minimum fol-
low-up of 2 years. This should provide robust data on both the clinical effectiveness and cost-effectiveness of this approach.

Currently, the strongest evidence for improved outcomes in remotely monitored patients using an implanted device comes from systems that can monitor pulmonary artery pressure. The COMPASS-HF study (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure), a randomized controlled study of the addition of data from an implanted hemodynamic monitor to the usual clinical review, reported a non-significant 21% reduction in heart failure hospitalizations or urgent care visits requiring intravenous therapy in 134 patients with advanced heart failure in the active arm compared with 140 patients randomized

![Image of implantable pulmonay artery pressure monitoring system](image)

**Figure 2.** The implantable pulmonary artery pressure monitoring system used in the CHAMPION trial.

Panel A. Implantable device. Panel B. Selective pulmonary angiogram showing the device’s position. Panel C. The patient is instructed to take a daily reading from home using the equipment. Panel D. The health care professional reviews the trends in the pulmonary artery pressure. Panel E. Trends in pulmonary artery pressure.

to the control arm. Pulmonary artery pressure was indirectly estimated by applying an algorithm to the measured right ventricular pressure.

Directly measuring pulmonary artery pressure is even more useful. Recent data from the CHAMPION study (CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA class III heart failure patients), which used data collected from an implanted wireless pulmonary artery pressure monitoring device in heart failure patients with reduced or preserved ejection fraction, show a 30% reduction in heart failure hospitalizations over 6 months (P<0.001) in patients with NYHA class III. In this study, patients transmitted their pulmonary artery pressure daily and physicians targeted an acceptable range of pressure, with increased use of diuretic and oral nitrates (and other medications) at the discretion of the monitoring physicians in the remotely monitored arm (Figure 2).

WHAT IS THE COST OF TELEMONITORING?

Despite the inclusion of cost savings as a political rationale for telecare, there are few reports on the cost of telemonitoring. When studies report the cost of telemonitoring, it varies considerably according to the health care setting and the components of both “usual” care and telemonitoring. Our experience with telemonitoring in the Home-HF study in West London, UK suggests a mean incremental cost of GBP £1600 (US $2500) per patient for telemonitoring over 6 months, although there were no statistically significant differences in the overall costs between the telemonitoring arm and the usual care arm of the study. In a decision-analysis model of cost-effectiveness for patients recently discharged from the hospital after a heart failure exacerbation, another UK analysis, based on a network meta-analysis, reported an incremental cost-effectiveness of GBP £11 873 (US $18 550) per quality-adjusted life year, representing a reasonable value for the money, but increased expenditures would be needed to reap the benefits. Important questions remain about the optimal model of monitoring and the patients most likely to benefit. The cost and organizational changes required to run such a service appear to be substantial and may not be good value for money.

To have a higher value for the money, the home monitoring equipment should be inexpensive and an individual service should monitor a larger number of patients, however, there are likely to be limits on how many patients a single health care professional can follow at any point in time.

A recent survey of cardiologists in the European Union involved with the European Heart Rhythm Association Electrophysiology Research Network identified a lack of reimbursement (80% of 43 centers) as a major barrier to the introduction of remote monitoring services for patients with implanted devices in Europe. Additional workload was also identified as a significant barrier, although most cardiologists considered remote monitoring a clinically useful practice, with significant benefits for patients and health care organizations.

WHAT DO PATIENTS THINK OF TELEMONITORING?

Patients with heart failure indicated that a major issue in their care was the need for better access to specialist advice, including an identified contact who is familiar with their medical condition. This wish can be partially addressed through telemonitoring, which directly and indirectly increases contact with the health care professional and leaves the patient and their family less isolated. When help is sought, the health care professional has easy access to up-to-date clinical information upon which to base their advice. In addition, the patient gains confidence that if there is a medical problem, the health care professional is likely to contact them, rather than worrying about whether or not to contact the health care professional.

Despite concerns about the feasibility of home-based technology to monitor chronic conditions, particularly in the elderly, patients generally find the equipment easy to use, with some studies reporting >80% usage.

PRACTICALITIES OF TELEMONITORING

International guidelines for heart failure care suggest early (within 2 weeks) face-to-face follow-up after hospitalization, education to facilitate self-care, and ongoing support from a multiprofessional team that is responsive to the patient’s needs. The highest risk period for rehospitalization is in the first few weeks after discharge from the hospital. If telemonitoring is to be conducted for such patients, it should be installed as soon as possible following hospital discharge and the patient should be instructed in its use.

The optimal time for telemonitoring is unclear. The follow-up in telemonitoring studies has ranged from 90 days to >12 months. In our experience, the greatest amount of
telemonitoring data outside preset limits occurs during the first 90 days of monitoring, which is reduced by ≈50% over the subsequent months.

However, it is particularly during these latter months that telemonitoring helps patients understand more about their heart failure and the actions required for self-care. In practice, most telemonitoring services enroll patients for at least 6 months following discharge, with an evaluation of its usefulness conducted at 30-day intervals thereafter.

International guidelines for the use of telemonitoring in heart failure have not yet been developed. In their absence, it is likely that the heart failure nurse will remain central to the success of this new approach to care by triaging and responding to the data and maintaining contact with the lead clinician for heart failure. In some countries, the nurse is also able to prescribe medications, although policies vary between countries. Telemonitoring relies on the confidence and ability of the health care professional to interpret and use the information.

There is likely to be a steep learning curve associated with handling increased amounts of information regarding physiological parameters without visual cues from face-to-face contact.

**ORGANIZATION OF SERVICES**

Heart failure disease management services and studies of telemonitoring, while designed to provide follow-up after hospital discharge, have primarily been led by secondary care. Such models potentially strengthen the relationship between the patient and the secondary care–based specialist, perhaps at the expense of the primary care team.

Patients with heart failure are generally elderly with multiple comorbid conditions, and simultaneously, they are likely to be under the care of a number of health care professionals and can become confused when they receive care from such a broad range of practitioners.

The successful introduction of telemonitoring is likely to depend on a functional multi-disciplinary team. Ensuring close collaboration between all agencies involved when action is appropriate is likely to be more important than whether the initial triage of data is undertaken in primary or secondary care or even outsourced to a call center.

**CONCLUSIONS**

With an increasingly elderly population living with heart failure, the need for high-quality disease management programs to “reach out” to patients in their normal living environment is set to dramatically increase. Telemonitoring offers the opportunity to provide a modern approach to the monitoring of such patients. It enables the patient and professional to adopt a proactive approach for recognizing problems and resolving issues together and it reduces unnecessary travel to the hospital or cardiology clinic. Telemonitoring ensures that patients have close contact with someone who knows their current health status, provides easy access to specialist help, and aids in scheduling hospital admissions when needed.

The benefits extend beyond the early detection of clinical deterioration to optimizing medication and facilitating education for self-care. However, the evidence that it improves outcomes over and above the best usual practice is thin, and the available data suggest that, although it may improve outcomes, this will come at additional expenses and organizational disruption. Convenience and acceptability are high for the patients, but implementation remains slow due to a lack of reimbursement. The added value of remotely monitoring a large number of physiological parameters in patients with an implanted device remains unclear and further research is required.

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Gene therapy for heart failure: the end of the beginning?

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New therapies are required to improve myocardial function in patients with severe heart failure. Within the failing cardiomyocyte, a fundamental abnormality and potential therapeutic target is dysfunctional cellular calcium homeostasis and excitation-contraction coupling. Viral vector–mediated delivery and transduction of cardiomyocytes with a cardiac sarco(endo)plasmic reticulum Ca2+ ATPase type 2a (SERCA2a) transgene can recover electrophysiological properties and contractile function in animal models and in ex vivo human cardiomyocytes. However, a recent phase 2b study failed to show clinical benefit in heart failure patients. This article reflects on the experience to date and looks ahead to what is next in gene therapy for heart failure.

The worldwide burden of heart failure (HF) is large and increasing, driving an ongoing search for new disease modifying therapies. Cardiac gene therapy is a promising technique to tackle this unmet need. The classic form of gene therapy involves delivering therapeutic nucleic acid to the cell type of interest to correct loss of function of the gene of interest.

Studies to date have focused on the convergence of molecular pathways controlling excitation-contraction coupling, and specifically, on the cardiac sarco(endo)plasmic reticulum Ca2+ ATPase type 2a (SERCA2a) enzyme as the final common pathway. A long program of laboratory research generated a translational cardiac gene therapy program using a recombinant adeno-associated virus type 1 (rAAV1) to transduce cardiomyocytes with a copy of the human SERCA2a gene. This culminated in the CUPID-2 study (Calcium Upregulation by Percutaneous administration of gene therapy In cardiac Disease). The results from this study were much anticipated, but when they arrived, they were greatly disappointing. While there were no safety issues with infusion of the virus at the dose studied, the trial failed to identify any clinical benefit from treatment with AAV1 SERCA2a in patients with chronic HF.

Far from being the end of the story, this setback marks the end of a chapter in a story that will continue to develop. The CUPID program has blazed a trail, challenged the public’s and physicians’ perceptions about the practicability and safety of gene therapy, tested hypotheses about vector design and mode of delivery, and laid the foundation for future work. This review introduces cardiomyocyte calcium homeostasis as a target for gene therapy, reviews results from clinical trials to date, considers the reasons for the failure of the CUPID-2 trial to show efficacy, and on this basis, looks ahead to the future of gene therapy in HF.

CALCIUM AS A THERAPEUTIC TARGET

The HF syndrome is a progressive dysregulation of cardiovascular function that is usually initiated by a specific insult facilitated by an individual’s inherited susceptibilities, and perpetuated by maladaptive neurohormonal responses to the failing homeostasis, particularly by the sympathetic nervous system and the renin-angiotensin system. This dysregulation occurs at all levels from systems physiology, organ and tissue maladaptive remodeling, cellular dysfunction, and ultimately, to dysregulation of cardiac gene
expression. Extensive cell biology studies over the last 30 years have identified a number of proteins that appear central to this process. In the search for new HF therapeutics to combat the growing HF epidemic, gene therapy could target these alterations to gene expression and return the proteome to its healthy composition, helping to regain a normal physiological milieu. However, the challenge is to determine which gene to select and how to deliver it to the diseased human heart in a manner that increases the levels of functional target protein to modify the underlying disease effectively.

Calculated is central to excitation-contraction coupling, cellular electrophysiology, signaling, and even gene expression itself. At the cellular level, the final common pathway of all HF syndromes involves a malfunction in SERCA2a calcium handling, and in particular, a reduction in the expression and activity of cardiac SERCA2a (the SERCA2a isoform is predominant in the cardiomyocyte sarcoplasmic reticulum [SR]). In healthy cardiomyocytes, depolarization of the cardiomyocyte triggers cardiac systole by opening voltage-gated (L-type) calcium channels and calcium influx into the cytosol. This, in turn, triggers an opening of ryanodine receptors (RyR) in the SR, and a much larger calcium flux from the SR into the cytosol, which initiates cardiomyocyte contraction. The speed and magnitude of the calcium flux determines the rate and force of contraction. Restoration of cytosolic calcium to baseline levels occurs in cardiac diastole through a combination of active transport from the cytosol back to the SR and into the extracellular space, both against calcium concentration gradients. The former occurs by the action of SERCA2a in the SR membrane and the latter occurs via a Na+/Ca2+ exchanger (NCX) in the cell membrane.

SR calcium reuptake is under tight physiological control to facilitate adjustments to inotropy, chronotropy, and relaxation kinetics, particularly via changes to the phosphorylation status of the protein phospholamban, which associates with SERCA2a and modulates its function. SR calcium reuptake is also regulated by posttranscriptional regulation of component gene expression (eg, by noncoding RNAs, such as microRNA-25), posttranslational modifications to SERCA2a (eg, by small ubiquitin-like modifier [SUMO] proteins), protein-protein interactions (eg, with S100A1, which regulates the activity of SERCA2a and RyR), and redox regulation. However, in the failing cardiomyocyte, a combination of factors reduce SERCA2a activity and impair cytosolic calcium clearance. This leads to the following: (i) increased end-diastolic cytosolic calcium that causes impaired cardiomyocyte relaxation, and in particular, slower rates of relaxation and stiffness; (ii) depletion of SR calcium stores, causing reduced systolic RyR calcium flux and systolic impairment; and (iii) compensatory mechanisms, such as RyR leakage and upregulation of NCX, leading to electrical...
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Approaches to directly increase SERCA2a expression have been extensively reviewed elsewhere. Briefly, studies in isolated human cardiomyocytes and animal models using viral vector transduction with the SERCA2a transgene show normalization of calcium fluxes, correction of cell contractile properties, and improvements in overall cardiac function with a reduction in left ventricular (LV) volumes (Figure 1). Furthermore, in contrast with other positive inotropes that are typically proarrhythmic, preclinical studies from our lab and others demonstrate that SERCA2a gene therapy improves myocyte energetics and reduces the propensity for ventricular arrhythmias. Multiple mechanisms may explain the observed antiarrhythmic effects (Figure 2, page 48).

Vector choice

To achieve target protein (e.g., SERCA2a) expression at levels sufficient to influence myocardial biology and organ function, the transgene must reach the myocardium, bind to and enter individual cardiomyocytes, be transported into the cell nucleus, and be recognized by the host transcriptional complexes. Viruses are a natural example of these biological steps being achieved in an efficient manner. Viral vectors remain the most commonly used vector above nonviral alternatives, such as microparticles that have to be engineered to enter cells and cooperate with translation, or naked plasmid DNA that, although non-pathogenic and mildly immunogenic, is largely destroyed by lytic enzymes before reaching the cell nucleus and results in a lower efficiency. Several viruses carry a pre-evolved predilection for specific cell types, and as a result, can facilitate tissue targeting despite a straightforward systemic administration. AAVs, adenovirus, lentiviruses, and retroviruses have all been studied as candidate vectors.

Disadvantages of viruses are prominently related to their immunogenicity. Recognition of viral antigens potentially stimulates both antibody- and cell-mediated responses, which clinically presents in a wide spectrum of responses from asymptomatic seroconversion to a severe systemic inflammatory response. In an early dose-escalation study using an adenovirus vector for ornithine transcarbamylase deficiency, one subject receiving the highest dose developed a severe inflammatory response, which led to multiorgan failure and death. This reflects the immunogenic effects of adenovirus as a common pathogen. Moreover, while viruses can have tropism for specific organs or cells and can be physically delivered to specific body compartments, off-target transfection of other tissues is common and has the potential to provoke inadvertent, off-target side effects. Aside from the deleterious systemic effects of an acute immune response, the genesis of antcapsid antibodies and specific memory T cells may prevent the

Figure 1. Abnormal contraction profiles and calcium transients are corrected after SERCA2a gene transfer.

Human cardiomyocytes from failing (left, right) and nonfailing (center) hearts were obtained and studied in isolation. Failing cardiomyocytes show reduced velocity and amplitude of cell shortening compared with nonfailing cardiomyocytes, which was associated with a prolonged calcium transient. Isolated cells were treated with an experimental adenovirus containing the SERCA2a transgene, and 24-hours postinfection the cells showed a normalization of contractile properties and calcium transient duration. Fura-2 ratio is a measure of intracellular calcium.

Abbreviations: SERCA2a, sarcoplasmic reticulum Ca2+ ATPase type 2a.


instability and a greater propensity for ventricular arrhythmias. This combination is evident in isolated cardiomyocytes where contraction occurs with lower amplitude and slower onset (Figure 1).

Restoring activity of SERCA2a might be one strategy to augment function in the failing cardiomyocyte. This could be achieved by directly increasing SERCA2a expression, by enhancing SERCA2a activity, by increasing the expression of factors that enhance its activity (e.g., the SUMO proteins), or by removing factors that inhibit its function (e.g., unphosphorylated phospholamban). Translational gene therapy programs in HF have, to date, focused on approaches to directly increase SERCA2a expression.

CLINICAL TRIALS WITH AAV1.SERCA2A

The laboratory data supporting strategies to directly increase SERCA2a expression have been extensively reviewed elsewhere. Briefly, studies in isolated human cardiomyocytes and animal models using viral vector transduction with the SERCA2a transgene show normalization of calcium fluxes, correction of cell contractile properties, and improvements in overall cardiac function with a reduction in left ventricular (LV) volumes (Figure 1). Furthermore, in contrast with other positive inotropes that are typically proarrhythmic, preclinical studies from our lab and others demonstrate that SERCA2a gene therapy improves myocyte energetics and reduces the propensity for ventricular arrhythmias. Multiple mechanisms may explain the observed antiarrhythmic effects (Figure 2, page 48).
therapeutic virus from transducing the target cell, thus limiting its effects both in subjects who have previously received the recombinant virus and in subjects who have previously encountered a wild type virus displaying similar capsid antigens. This has important implications for retreatment, if required, in individuals and for potential benefit in populations with high rates of existing immunity. In general, adenoviruses have shown greater immunogenicity than other candidate vectors, in particular, compared with the nonpathogenic AAV.

Another concern with viral vectors is the potential for insertional mutagenesis resulting from recombination of the transgene with the host genome, which risks initiating cancer. Again clinical trials yield direct experience. Trials of a retroviral gene transfer for severe combined immunodeficiency (SCID-X1) showed initial promise, but these trials were stopped after the emergence of a clonal T-cell population in 2 patients at 3 years posttransfection, occurring due to transgene integration near an oncogenic promoter region. This is a major concern for integrating vectors, including retroviruses and some lentiviruses.

Despite these specific limitations, viruses are currently the best vector for administration of gene therapy. Historically, the adenovirus has been favored and is still efficient as a laboratory tool, but more recently, AAVs have come to the fore. AAVs are small (25 nm, 4.7 kb), nonenveloped viruses from the Parovirus family. A total of 12 human serotypes have been identified (AAV1 to AAV12). The specific characteristics that make AAVs preferable in cardiac gene therapy are:

1. Low pathogenicity. AAV does not cause a recognized disease in humans and requires coinfection with an adenovirus or herpesvirus to replicate;
2. AAV elicits only a mild and predominantly antibody-mediated immune response;
3. There is a predilection of AAV serotypes 1, 6, 8, and 9 to transduce cardiac and skeletal muscle, thus targeting the transduction to the tissue of interest;
4. Wild type AAV (wtAAV) can integrate into the host genome, but rAAV persists in the nucleus as a stable episomal concatamer, with very low rates of integration, which greatly reduces the risk of insertion-
Stage 2 was a randomized, controlled, double-blind study to evaluate the low-, mid-, and high-dose cohorts, which were compared with a blinded, placebo-controlled group receiving a sham infusion. The LVEF criterion was relaxed to <35% and the maximal oxygen consumption to <20 mL/kg/min. Crucially, the investigators adjusted the inclusion criteria regarding NAb status, such that henceforth only patients with absent NAb levels (titer <1:2) could be enrolled. This was on the basis that, in stage 1, the clinical status of 2 patients quickly deteriorated and LV assist device (LVAD) implantation and cardiac transplantation were required. The subsequent examination of excised myocardial tissue using quantitative polymerase chain reaction assays showed an absence of the SERCA2a transgene, suggesting neutralization of the rAAV vector by preexisting NAbs prior to successful transduction. The key result was a dramatic screening dropout caused by the presence of NAbs. Of the 509 patients screened, 265 patients (52%) were excluded due to NAbs. After other exclusions, 39 patients were enrolled in stage 2 (Figure 3, page 50).
The key finding was confirming safety in these small patient numbers, as patients in all arms of the study suffered expected adverse events related to HF, without complications attributable to the gene therapy product or its administration. The occurrence of HF adverse events was lower with an increasing dose of the study drug, suggesting a possible dose-related efficacy. While this study was relatively small and the prespecified primary end point was incidence and severity of adverse events, potential efficacy was further evaluated in the report of this data at the 12-month follow-up.

The investigators studied multiple end points. First, they studied the change in 7 markers of HF clinical efficacy at 6 months by individual and by group, and they assessed clinical outcomes using the Kaplan-Meier approach. The efficacy markers were grouped into 4 domains of efficacy: symptomatic (NYHA class and HF questionnaire), functional (6-minute walking distance and maximal oxygen consumption on cardiopulmonary exercise testing), biomarkers (natriuretic peptides), and structural (echo markers of remodeling). For the group analyses, a comparison of mean data was used, while a scoring system based on clinically meaningful changes was used for the individual analyses, highlighting concordant or discordant changes of the multiple variables. These parameters formed

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**Figure 3. Screening and enrollment in the CUPID-1 trial.**

For stage 2 of this trial, the accepted titer for NAbs was modified such that any patients with a titer ≥1:2 were excluded. Of the 509 patients screened, 52% were ineligible using this criterion.

**Abbreviations:** AAV, adeno-associated virus; CUPID, Calcium Upregulation by Percutaneous administration of gene therapy In cardiac Disease; DRP, D/Nase-resistant particles; NAb, neutralizing anti–AAV antibodies; SERCA2a, sarco(endo)plasmic reticulum Ca²⁺ ATPase type 2a.

the primary efficacy end point success criteria, which required any of the following: (i) improvement in at least 2 of the 4 efficacy domains in the group analysis with a $P<0.2$, with a numeric superiority of active vs placebo in all domains; (ii) improved score in the individual efficacy analysis with a $P<0.2$, or (iii) improved time to event in the Kaplan-Meier analysis. Second, they studied the occurrence of recurrent clinical events as a marker of clinical outcome, using a joint frailty model to account for factors often confounding standard outcome tests. The joint frailty model allows the analysis to account for the number of clinical events (eg, number of HF hospitalizations rather than the time to first hospitalization), varying severity of clinical events (eg, cardiovascular death vs HF hospitalization), and the effect of terminal events on the risk of further clinical events (ie, early death prevents further hospitalizations).

Using these criteria, the primary efficacy outcome was met. Patients receiving high-dose therapy showed stabilization of their HF compared with patients receiving placebo who showed progressive HF deterioration. In the individual-level analysis, there was a significant improvement in the individual efficacy score in high-dose vs placebo groups (which alone was sufficient to meet the primary outcome criteria). In the group-level analysis, there was an improvement in active vs placebo groups in 3 out of 4 domains (though not exclusively in the high-dose group). The outcome end point was met with a significant reduction in the duration of cardiovascular hospitalizations in placebo vs high-dose groups.

CUPID-1 confirmed the safety of AAV1.SERCA2a delivery in patients with advanced HF at 12 months, which has been reiterated at 36 months in this small initial cohort. This report also provided further evidence of a persistent efficacy benefit in high-dose vs placebo groups with the joint frailty model method showing an 82% reduction in recurrent cardiovascular events adjusted for individual frailties (ie, susceptibility to recurrent events) and correlated with terminal events (hazard ratio [HR], 0.18; $P=0.048$, Figure 4). A total of 13 of the 39 patients had died after 3 years of follow-up, none related to the gene product or its administration, and there was a numerically, but not statistically, greater chance of survival in patients treated with high-dose therapy vs placebo.

Potential limitations of CUPID-1 relate to the inferences about efficacy that can be drawn from the data, and these have received close attention since the neutral CUPID-2 trial report. It is important to emphasize that the CUPID-1 investigators clearly acknowledged that the trial was small and designed only to demonstrate safety, and the report correctly discusses efficacy with clear statements about the limitations of available data. Beyond this, commentators have questioned the matching of baseline HF severity between the experimental groups. The report does not perform statistical comparisons of baseline characteristics, but numerically, patients in the placebo group have higher N-terminal pro–brain natriuretic peptide levels (NT-proBNP), lower LVEF, lower peak VO$_2$, and greater incidence of preexisting additional cardiovascular conditions in comparison with the AAV1 SERCA2a groups (Table 2 in the main body of the Jessup et al report and Table 10 in its supplementary data). This imbalance is particularly apparent in the high-dose group. In addition, recruitment to the high-dose group only commenced after 15 patients had already been recruited to placebo, low-dose, and mid-dose groups.
This delay was appropriate and prespecified due to the dose escalation in stage 1, such that complete safety data for the high-dose cohort was awaited when stage 2 recruitment started. Together, these factors imply that any apparent clinical benefit, specifically the dose relationship (ie, added benefit of the high dose vs low dose or mid dose), may also be partly explained by baseline imbalances, procedural experience, and study progression rather than a treatment effect.

The methodology has come under some scrutiny. Proponents of the stated primary efficacy outcome would argue that its three strands (group, individual, and clinical outcome) and its emphasis on concordance of efficacy outcomes provide greater specificity and allow the statistical testing to accept the less rigorous \( P < 0.2 \) level used as the test for significance, and would argue that the joint frailty model carries important advantages over Kaplan-Meier outcome analyses as outlined above. However, detractors might make the following comments: (i) in the symptom and functional criteria, it is the least robust measure that provides the significant result (for symptoms, the subjective assessment of NYHA class is significant, but an objective HF questionnaire shows no difference; in the functional testing, the submaximal 6-minute walking test shows significant change, but maximal oxygen uptake as the gold standard measure shows no difference), (ii) in the group-level analysis, the domain success criteria generalize to active vs placebo and actually rely on the low-dose group as much as the high-dose group to meet the primary end point, where the authors’ conclusions emphasize a dose-related relationship and improved efficacy in the high-dose group; and (iii) there is justification for using \( P < 0.2 \) for the individual efficacy scores where there are multiple sorting criteria and statistical controls, but this is less clear for the group-level analysis, where the statistical power is weaker simply due to the small number of patients.

In summary, CUPID-1 certainly provided evidence for feasibility and safety of using AAV1.SERCA2a in patients with advanced HF, which justified progression to larger clinical studies to examine the product’s clinical efficacy in more detail.

**CUPID-2 trial**

Drawing on the experience from the CUPID-1 trial, the investigators set out to demonstrate clinical efficacy of AAV1.SERCA2a in patients with advanced HF.\(^3\) CUPID-2 was a phase 2b, double-blind, randomized, placebo-controlled trial that allocated patients 1:1 to receive placebo or high-dose AAV1.SERCA2a (\( 1 \times 10^{13} \) DNase-resistant particles).\(^32\) All patients with Nab titers \( \geq 1:2 \) were ineligible (which, similar to CUPID-1, excluded 9\% [921/1558] of patients initially screened). The trial used a joint frailty model for the primary outcome to properly account for the burden of recurrent HF events, similar to CUPID-1, and there were strict HF severity criteria (LVEF < 35\%, hospitalization for HF within the previous 6 months, and high brain natriuretic peptide levels within the previous 30 days) to ensure a high rate of clinical events. Recruitment concluded in June 2014 after enrolling 250 patients in 54 centers. Our institution was the lead UK center and the largest European recruiting site.

The results from the CUPID-2 trial are now available; however, they do not support the hypothesis that AAV1.SERCA2a is efficacious in patients with advanced HF on optimized medical and device therapy.\(^1,33\) In the final modified intention-to-treat population, 121 patients received treatment with AAV1.SERCA2a and 122 patients received placebo (total n=243). For the primary outcome, there were 232 recurrent events recorded—128 in the placebo group and 104 in the treatment group—equating to a nonsignificant 7\% risk reduction for recurrent HF events in the presence of HF terminal events in patients treated with AAV1.SERCA2a vs placebo (HR, 0.93; 95\% CI, 0.53-1.65; \( P = 0.81 \)). Similarly, there was no treatment effect evident for the powered secondary end points (all-cause death, need for a mechanical circulatory support device, or heart transplant) or exploratory end points (improvement in NYHA functional class, 6-minute walking distance, and quality of life [assessed by a questionnaire]). In the prespecified subgroup analyses, there were no subgroups where the results differed. Specifically, there was no sustained benefit seen in the nonischemic HF subgroup, patients who might have a better substrate for effective gene therapy. Importantly, no safety concerns were reported. Almost all participants were Caucasian males, but that aside, randomization achieved a good balance of baseline parameters between placebo and treatment groups, and an excellent proportion of participants were receiving the guidelines’ recommended HF therapies.

**Other clinical trials using AAV1.SERCA2a**

Three further studies were in progress in April 2015 when the initial findings from CUPID-2 were announced. However, at the time that this manuscript was prepared, two of these were suspended and one closed due to the neutral outcome.
of the CUPID-2 trial. None of the three studies had completed recruitment, so any data yielded will be incomplete, but nonetheless, they may provide further substance to the debate around CUPID-2.

**SERCA-LVAD trial**

The SERCA-LVAD trial (NCT00534703) was an investigator-led trial based at our institution and funded by the British Heart Foundation. At the time of writing this article, the trial had been suspended. This study aimed to test safety and efficacy in patients with long-term LVADs for chronic HF. Recruitment commenced in June 2014 and the first patient received the investigational medicinal product at Harefield Hospital on July 23, 2014. This was the first LVAD patient in the world to receive gene therapy for HF. The design was a two-center, double-blind, randomized, controlled trial that enrolled 24 stable patients with chronic HF treated with an LVAD and allocated these patients 2:1 to receive AAV1.SERCA2a or placebo. There were 4 goals of the study: (i) assess the safety and feasibility in LVAD patients (primary outcome); (ii) systematically assess the magnitude of SERCA2a gene expression in transfected patients using tissue from an elective percutaneous LV biopsy taken 6-months posttransfection; (iii) directly address the hypothesis that the presence of circulating NAbs blocks viral transduction, considering that all NAB positive patients were excluded from the CUPID-1 and CUPID-2 studies—here randomization was stratified to include both NAB positive and NAB negative patients in equal proportions in the active and placebo arms; and (iv) test the exploratory hypothesis that the effects of SERCA2a gene therapy might be magnified in the presence of optimal LV loading conditions facilitated by the LVAD.

**AGENT-HF trial**

The AGENT-HF trial (NCT01966887) was an investigator-led trial based in France, with the aim of further elucidating the reverse ventricular remodeling effects of AAV1.SERCA2a in ambulatory patients with HF. The study had a double-blind, randomized, placebo-controlled design and had planned to recruit 44 advanced HF patients without Nabs and use the same product and method of administration as previous studies. The primary outcome was LV end-systolic volume assessed by computed tomography, and secondary outcomes included various biomarkers and structural/functional tests. These detailed assessments conducted at a single institution would greatly assist interpretation of the CUPID-2 outcome data.

**High-dose trial**

A further phase 1/2 study (study of high-dose genetically targeted enzyme replacement therapy [MYDICTAR] for advanced HF; NCT02346422) was initiated by the Celladon Corporation in January 2015 to assess a higher dose administration of AAV1.SERCA2a. The study was planned in two phases similar to CUPID-1, with an initial, open-label phase followed by a phase of randomized, double-blind allocation. The “high dose” in the CUPID-1 and CUPID-2 studies was $1 \times 10^{11}$ DNase-resistant particles; however, in this study, DNase-resistant particles and dosing were planned to be 2.5-fold greater. The rationale was based on the observed dose-response in CUPID-1, such that the treatment effect could be multiplied by increasing the dose. This would have been important if CUPID-2 had shown either equivocal or clear efficacy. However, due to the neutral outcome from CUPID-2, this study has been closed.

**WHY DID CUPID-2 FAIL TO SHOW EFFICACY?**

These results undoubtedly represent a significant setback for the field, but reflect just the first chapter of a long story in developing gene therapy for HF. The key to going forward is to understand why the CUPID-2 trial yielded neutral results and how this understanding can be applied to future studies. The key factors to consider include: (i) the efficiency of SERCA2a transgene transduction into cardiomyocytes, particularly considering the choice of AAV1 as the delivery vector, the dose used, and the mode of administration; and (ii) the choice of the SERCA2a transgene as a target.

**Transduction efficiency: vector choice, dose, and mode of administration**

One explanation for the lack of efficacy could be that an insufficient quantity of the SERCA2a transgene is reaching an insufficient number of cardiomyocytes to appreciably alter functioning of the whole heart. Early indications suggest that there was an inadequate transduction of cardiomyocytes by the SERCA2a transgene due either to an inadequate number of viral particles reaching the cardiomyocytes or a poor transduction of the transgene by the viral vector. The physiological effects observed in animal models and isolated cells were associated with a several-fold greater increase in the copies of the SERCA2a gene than has been observed in tissue recovered from patients transfected in both CUPID studies. This implies that the rAAV1 vector was inefficient for delivering the transgene, that an inadequate dose of AAV1.SERCA2a was used, that the mode of administration was suboptimal, or that it was a combination of all three.
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The rAAV1 was adopted as a vector for strong reasons that were outlined earlier, with the main disadvantage being the high occurrence of NABs in the population. Certainly, data from the CUPID studies have confirmed its safety, and in particular, its low immunogenicity, which is reflected by the absence of inflammatory sequelae seen with other vectors, such as the adenovirus. However, it remains possible that the AAV1’s ability to transduce human cardiomyocytes is reduced in vivo. Further serotypes of AAV have been discovered or engineered since the CUPID program was initiated, and in particular, the AAV9 serotype may show greater efficiency in transduction and greater tropism for cardiac muscle, allowing larger doses to be used more efficiently. A new generation of so-called bioengineered nanoparticles (BNPs) may come to fruition, allowing further cardiac specificity and conferring other advantages, such as an enlarged genome size and a nontypical antigenic profile for AAVs (helping to avoid cross-reactive NABs). The dose used in CUPID-2 was the highest of the doses tested in CUPID-1 (1x10^{13} DNsar-resistant particles), and is equivalent to or exceeding the dose used in other AAV studies, but in the absence of safety concerns with this dose, there could be rationale to increase the dose (indeed there was a study planned to test 2.5x10^{13} DNsar-resistant particles, which has now been closed, NCT02346422).

The mode of vector delivery should also be reviewed. CUPID and associated studies all used a single anterograde intracoronary infusion, but there are different modes of delivery with their advantages and disadvantages. With a rAAV, the possible other routes could include: (i) peripheral intravenous infusion, which is beneficial for the patient and relies on the rAAV’s cell tropism to select cardiomyocytes, but suffers from the dilutional effect of the large circulating volume, (ii) retrograde infusion via the coronary sinus, which may allow controlled dwell times and prolonged exposure — this has been tested with good results in a large animal model, (iii) closed-loop recirculation, with the vector infused into the coronary artery and then drawn from the coronary sinus back to the coronary artery catheter via a cardiopulmonary bypass system for oxygenation, thereby increasing exposure time, (iv) direct intramyocardial injection (such as was used in the recent STOP-HF trial [Stromal cell-derived factor-1 plasmid Treatment for Patients with Heart Failure]; which can yield sustained transgene expression, but may only be in a limited cell number around the injection site, or (v) injection into the pericardial space.

Transduction efficacy by different routes was examined in animal studies, and while the anterograde coronary route initially showed modest results, subsequent studies with modifications (eg, greater virus concentrations, adjustments to catheter delivery systems, increased virus exposure time) yielded improvements and detailed toxicity and dosing assessments. Further efforts have included anterograde infusion with venous occlusion, ischemic preconditioning to increase vascular permeability, and concurrent glyceryltrinitrate infusion to prevent coronary vasospasm and achieve coronary vasodilation, though only the latter was adopted in the CUPID and associated studies.

Is SERCA2a the correct target?

The SERCA2a enzyme is the final common pathway of a complex molecular network and its activity is subject to control by other factors. While data from animal studies and ex vivo human cardiomyocytes support direct transduction of the human SERCA2a gene into cardiomyocytes as a therapeutic approach, if the cellular milieu is already downregulating SERCA2a activity, the exogenous SERCA2a may be subject to the same processes. This could explain the lack of observed effect.

One such SERCA2a modulator is phospholamban, which complexes with SERCA2a and inhibits its activity, most potently when in its dephosphorylated form. In turn, the phosphorylation state of phospholamban is determined by the balance of kinase activity (particularly protein kinase A, whose activity is upregulated via β-adrenergic activity) and phosphatase activity (particularly protein phosphatase-1 [PPI-1], whose activity is downregulated by the modulator molecule inhibitor 1c [I-1c]). In HF, the SERCA2a-phospholamban ratio is reduced with a relatively higher preponderance of dephosphorylated phospholamban. I-1c activity is decreased, and β-receptor signaling is desensitized. Conversely, signs of therapeutic benefit have been seen by blocking phospholamban with RNA interference in a rat HF model, increasing I-1c activity using AAV9- or BNP-mediated I-1c gene delivery in a pig HF model, delivering of the G protein-inhibitory peptide β-adrenergic receptor kinase C-terminus (BARKct) via AAV6 in a pig HF model, and overexpressing adenylyl cyclase-6 in a mouse HF model.

Some of these approaches are already in clinical program development (discussed below). Notably, development of direct phospholamban inhibitors for clinical use...
<table>
<thead>
<tr>
<th>Trial</th>
<th>Transgene</th>
<th>Vector</th>
<th>Dose delivered (VP unless stated)</th>
<th>Mode of delivery</th>
<th>Phase</th>
<th>Trial design</th>
<th>Comments</th>
<th>Current status</th>
<th>Ref.</th>
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<tr>
<td>CUPID-1</td>
<td>SERCA2a</td>
<td>AAV1</td>
<td>Very low, low, mid, or high dose (1 x 10^4, 6 x 10^2, 3 x 10^2, or 1 x 10^1)</td>
<td>Single anterograde intracoronary infusion</td>
<td>1/2a</td>
<td>Phase 1: open-label, dose-escalation (n=12); Phase 2: double-blind RCT using high dose (n=39)</td>
<td>First human HF gene therapy study</td>
<td>Completed</td>
<td>Confirmed safety, suggestion of efficacy</td>
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<td>First-in-man SDF-1 trial</td>
<td>SDF-1 Plasmid form</td>
<td>Low, mid, or high dose (5 mg, 15 mg, or 30 mg)</td>
<td>Endomyocardial injection to infarct border zone</td>
<td>1</td>
<td>Dose-escalation study (n=17)</td>
<td></td>
<td>Completed</td>
<td>Confirmed safety, suggestion of efficacy</td>
<td>44</td>
</tr>
<tr>
<td>AC6 gene transfer for chronic HF</td>
<td>AC6 AdV5</td>
<td>3 x 10^10 to 1 x 10^11 in 5 dose groups</td>
<td>Single anterograde intracoronary infusion</td>
<td>1/2a</td>
<td>Initial dose-escalation phase, then RCT 3:1 (n=56)</td>
<td></td>
<td>Reporting</td>
<td>Results expected 2015/2016</td>
<td>49</td>
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<tr>
<td>CUPID-2</td>
<td>SERCA2a</td>
<td>AAV1</td>
<td>1 x 10^11</td>
<td>Single anterograde intracoronary infusion</td>
<td>2b</td>
<td>Double-blind RCT (n=240)</td>
<td>Only ischemic HF patients included.</td>
<td>Completed</td>
<td>Failed to show efficacy</td>
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<td>STOP-HF</td>
<td>SDF-1 Plasmid form</td>
<td>15 mg or 30 mg</td>
<td>Endomyocardial injection to infarct border zone</td>
<td>2</td>
<td>Double-blind RCT (n=196)</td>
<td>Detailed imaging assessment for functional improvement</td>
<td>Completed</td>
<td>Failed to show efficacy</td>
<td>42,43, 50</td>
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<td>AGENT-AF</td>
<td>SERCA2a</td>
<td>AAV1</td>
<td>1 x 10^11</td>
<td>Single anterograde intracoronary infusion</td>
<td>2b</td>
<td>Double-blind RCT (planned n=44)</td>
<td></td>
<td>Suspended</td>
<td>after CUPID-2 results</td>
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<tr>
<td>SERCA-LVAD</td>
<td>SERCA2a</td>
<td>AAV1</td>
<td>1 x 10^11</td>
<td>Single anterograde intracoronary infusion</td>
<td>2a</td>
<td>Double-blind RCT (planned n=24)</td>
<td>First use of gene therapy in LVAD patients; first delivery to patients with AAV1 Nab+</td>
<td>Suspended</td>
<td>after CUPID-2 results</td>
</tr>
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<td>Higher dose AAV1</td>
<td>SERCA2a</td>
<td>AAV1</td>
<td>2.5 x 10^11</td>
<td>Single anterograde intracoronary infusion</td>
<td>1/2a</td>
<td>Phase 1: open-label; Phase 2: double-blind RCT (planned n=36)</td>
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<td>Closed after</td>
<td>CUPID-2 results</td>
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<tr>
<td>First-in-man inhibitor 1-c trial</td>
<td>AAV2/B (BNP)</td>
<td>Very low, low, mid, or high dose (3 x 10^10, 1 x 10^9, 3 x 10^9, or 1 x 10^8)</td>
<td>Single anterograde intracoronary infusion</td>
<td>1/2a</td>
<td>Phase 1: open-label; Phase 2: double-blind RCT (planned n=45)</td>
<td>BNP to overcome Nab and improve cardiac tropism; Highest planned dose is 100-fold higher than CUPID trials</td>
<td>Planning stage</td>
<td>Target phase 1 to start first quarter 2016</td>
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<td>First-in-man S100A1 trial</td>
<td>S100A1 AAV9</td>
<td>Not yet specified</td>
<td>Retrograde infusion via coronary sinus</td>
<td>1</td>
<td>Not yet specified</td>
<td>Retrograde infusion may increase uptake</td>
<td>Planning stage</td>
<td>Expected start date 2016</td>
<td></td>
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Table 1. Completed, ongoing, and planned gene therapy trials in human heart failure.

**Abbreviations:** AAV, adeno-associated virus; AC6, adenylyl cyclase type 6; AdV, adenovirus; AGENT-HF, AAV1-CMV-Serca2a Gene Therapy trial in Heart Failure; BNP, biological nanoparticles; CUPID, Calcium Uregulation by Percutaneous administration of gene therapy in Cardiac Disease; HF, heart failure; LVAD, left ventricular assist device; Nab, neutralizing anti–AAV antibodies; RCT, randomized controlled trial; SDF-1, stromal cell-derived factor 1; SERCA2a, sarco(endoplasmic reticulum Ca^2+ ATPase) type 2a; SERCA-LVAD, investigation of the safety and feasibility of AAV1-SERCA2a gene transfer in patients with chronic heart failure and a Left Ventricular Assist Device; STOP-HF, Stromal cell-derived factor-1 plasmid Treatment | Or Patients with Heart Failure; VP, viral particles.
has been slowed after observing a severe HF phenotype in humans with a sporadic loss-of-function mutation in phospholamban.\textsuperscript{48}

Separately, the molecules SUMO-1 and S100A1 (a small calcium-binding protein) have roles regulating SERCA2a activity. Sumoylation by SUMO-1 at specific and conserved sites causes posttranscriptional modification of the SERCA2a enzyme to increase its activity and stability. Levels of sumoylated SERCA2a are reduced in HF, and SUMO-1 gene delivery using AAV9 restores function in a pressure overload model in mice.\textsuperscript{8} S100A1 is downregulated in HF and regulates SERCA2a activity and RyR activity in the SR membrane. S100A1 gene transfer using an AAV6 vector has shown signs of efficacy in small and large animal models.\textsuperscript{40}

All of these factors (and many others) could have impinged on the success of direct SERCA2a gene transfer in the CUPID-2 study, and equally, could form targets for indirect modulation of SERCA2a activity. However, none can be taken completely separate from the next: they form a complex network of interactions, which will all be vulnerable to reciprocal regulation that could blunt clinical efficacy. However, for the time being, SERCA2a remains a very attractive option for clinical gene therapy for HF.

**WHAT IS NEXT IN THE CLINICAL PIPELINE?**

While the community continues to reflect on results from CUPID-2, there are already a variety of further gene therapy paradigms ready for clinical evaluation (Table 1, page 55).\textsuperscript{1,22,27,29,30,36,42,43,49,50} The I-1c and S100A1 trials should commence shortly, and the investigators of these trials should be congratulated for their program development and persistence in light of the CUPID-2 trial results.

A few general challenges should be kept in mind. First, it will be important to ensure clarity of scientific effect with new trials: already the next trials planned are changing several variables at once (eg, the S100A1 trial will use a different vector, different transgene, and different delivery route compared with the AC6 trial [Adenyl cyclase type 6 gene transfer for chronic HF].\textsuperscript{49} SDF-1 trial [Stromal cell-Derived Factor gene transfer for HF],\textsuperscript{50} and CUPID trials). While the novel approaches may be valuable, the risk is that understanding and integrating the outcome data with other trials could become more challenging.

Second, the challenge of preexisting NAbs remains. In the case of AAV1, this seems to occur in around 60% of patients, and is particularly problematic due to cross-reactivity of antibodies to AAVs of varying serotypes. Currently, the paradigm is to exclude these patients from trials, which could significantly impede widespread clinical uptake. Various approaches to combat NAbs are being studied, such as plasmapheresis and bioengineering the AAV capsid to alter its antigenic regions as with the BNP AAV2i8 proposed for the I-1c study,\textsuperscript{17,51} and these ideas warrant further investigation. Finally, the importance of investor funding for these innovative programs should not be underestimated, and we would encourage all investors to have patience and continue to support the development of effective clinical gene therapy programs. While we have come a long way already on the journey from the laboratory to the first clinical trials, we have only completed the first chapter of the clinical development of gene therapy for HF, which we hope one day will deliver important benefits to the health of our patients.

**CONCLUSION**

Gene therapy for HF illustrates the scientific transitional journey through scientific hypothesis, laboratory experimentation, and translation to clinical trials. Much progress has been made, though many unanswered questions and unmet challenges remain. What is certain is that SERCA2a gene transfer has a logical and coherent body of laboratory evidence in its support, and the onus is now on the clinical research community to understand and overcome the current limitations.\textsuperscript{7} There are plenty of questions to be addressed regarding SERCA2a gene transfer, but in many ways, the story is only just beginning.

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58
This brief review will describe the current therapeutic status of angiotensin receptor antagonists, placing them in the context of the evolving understanding of the renin-angiotensin system. A description of the renin-angiotensin system was described in a previous article in 2001. Since then, the physiological importance of the autocrine and paracrine actions of angiotensin and its metabolites has fundamentally changed the nature of the renin-angiotensin system from being that of just an enzyme cascade generating circulating angiotensin II to one that includes a renin-based system found in many tissues and organs.

In order to describe the different angiotensin antagonists, it is necessary to summarize the metabolic pathways that produce different angiotensins (Figure 1). Angiotensins are generated from angiotensinogen, the 14 amino acid parent peptide. Angiotensinogen is present in both plasma and tissues and it is synthesized in the liver. Angiotensin I, a 10 amino acid peptide, is generated by either the circulating aspartate-protease enzyme renin or cathepsins in the tissue (lysosome serine proteases). There are three enzyme isoforms, including the δ-isof orm that is present in the cardiovascular system and the γ-isof orm that is found in neutrophils. Tonin, an additional tissue serine protease, forms angiotensin II, an 8 amino acid peptide, from tissue angiotensinogen.

Figure 1. Angiotensin peptide formation.
Abbreviations: Ang, angiotensin; APA, aminopeptidase A; APN, aminopeptidase N; AT4R, angiotensin type 4 receptor; MasR, Mas receptor; NEP, neutral endopeptidase (neprilysin); POP, prolyl endopeptidase; (P) RR, prorenin receptor; TOP, thimet oligopeptidase.


Keywords: angiotensin receptor antagonist; angiotensin II receptor; G protein-coupled receptor
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ther discussed, but the nature of the angiotensin subreceptors and specific antagonists will now be described.

Angiotensin II type 1 receptor (Figure 2) activation by angiotensin II causes a range of intracellular responses due to the activation of receptor-specific G proteins. It is now clear that the angiotensin receptor can be activated by mechanical, nonpeptide, and peptide signal mediators. The G proteins that interact with angiotensin I include G₁, G₁₁_, and G₁₁. Activation of these subreceptor types results in a range of intracellular downstream effects, including calcium release, diacyl glycerol signaling, etc. Given the range of tissue responses to angiotensin (Figure 1), the rationale for seeking specific inhibitors of their receptors for therapeutic purposes is clear.

**INITIAL DISCOVERIES**

In the mid-1950s, Peart first identified angiotensin and called it “hypertension,” though subsequently this was changed to angiotensin II. Gross, working in Ciba, showed that angiotensin II stimulated aldosterone release from the adrenal cortex. The identification of nonpeptide angiotensin II antagonists enabled clinical scientists to explore the actions of angiotensin II in many experimental and clinical situations. The first angiotensin II antagonist to be discovered was saralasin in 1971. Saralasin was a close analogue of angiotensin II, where the asparagine, isoleucine, and phenylalanine at positions 1, 5, and 8 were replaced with a sarcosine, valine, and isoleucine (Sar₁, Val₃, Ala₈). Other analogues with substitutions in the 8th position of angiotensin II were also synthesized. The initial research leading to the discovery of saralasin was performed in the Norwich–Eaton pharmaceutical company (US) by Pals et al.
tial research strategy was to identify compounds that would block different elements of the renin-angiotensin system by inhibiting three potential reactions: (i) renin release; (ii) the conversion of angiotensin I to angiotensin II by carboxypeptidases; or (iii) the vascular contractile actions of angiotensin II. In retrospect, these were ambitious aspirations. Subsequently, this group focused on angiotensin II antagonists, partly because the synthesis of these peptides, based on the known structure of angiotensin II, was easier than the other biological targets. Furthermore, there was a well-characterized in vitro rabbit aortic vascular muscle system that contracted to angiotensin II; therefore, the system could be used to detect antagonists of angiotensin II vasoconstrictor actions. They discovered that the Sar1, Val3, Ala8 analogue of angiotensin II blocked the contractile actions in the rabbit model. This reaction was potent (pA2=8.61) and selective because it did not block responses to noradrenaline or histamine. This peptide analogue, now called saralasin, which ironically had been their first synthesized compound, was taken into clinical trials after regulatory approval.

In clinical studies, responses to saralasin correlated with renin levels in patients when infused for 30 min with saralasin (10 µg/kg). Patients with low renin levels who were infused with saralasin showed a large pressor response, which was attributed to the partial agonist properties of saralasin acting on unoccupied angiotensin II receptors. However, in patients with high renin levels, saralasin caused a large depressor response, which was attributed to the blockade of angiotensin II receptors.

While saralasin could be used as a diagnostic test for assessing an individual patient’s renin status, it could not be used as an antihypertensive agent because it was not orally active and, more importantly, it was only a partial agonist and not a full antagonist. One of the somewhat complex properties of many G protein-coupled receptors is that of inverse agonism, often detected more easily in mutated G protein-coupled receptors. This somewhat counterintuitive phenomenon of either antagonism or agonism, depending on the experimental conditions, is discussed at length by Miura S et al.

ORALLY ACTIVE ANTAGONISTS

The increasing concerns of clinical cardiologists about the potentially harmful effects of excess activation of the renin-angiotensin system, such as acute myocardial infarction and stroke, made antagonism of the endogenous effects of angiotensin II an attractive drug target.

Figure 3. Structural modifications to the S-8307 and S-8308 compounds to develop losartan and eprosartan.

In the early 1980s, scientists in the Takeda Laboratories (Japan) patented two compounds (S-8307 and S-8308) claiming a mild antihypertensive effect that was attributed to binding at the angiotensin II receptor. As far as is known, these were serendipitous observations that were noted in the DuPont Merck pharmaceutical company (US) by a drug discovery group led by “Hank” Timmerman who joined the company from the Department of Pharmacology, University of Leiden (Holland).

While the Takeda compounds provided a valuable clue as to the structural requirements for angiotensin II receptor antagonism, a program of structural and functional studies was carried out in the DuPont Company using the Takeda compounds as basic models. This led to the discovery of the angiotensin II receptor blocker losartan, which was potent, selective, and orally active. Losartan was a selective antagonist of the angiotensin II G protein-coupled receptor.

Medicinal chemists used nuclear magnetic resonance techniques to obtain details of the structures of S-8307 and S-8308. A range of different chemical substitutions was applied to these basic structures to improve the specificity and oral activity, which led to the discovery of losartan in 1986 (Figure 3, page 61).12

Losartan was originally known by the number DuP 753. DuP 753 was carefully evaluated in a range of pharmacological tests that are summarized in Table I.13 In essence, DuP 753 was a potent, orally active, specific angiotensin II antagonist with a long duration of action.14 This latter property was subsequently, and serendipitously, attributed to the formation of EXP3174, a 5-carboxylic substituted analogue and active metabolite of DuP 753.15 DuP 753, which was subsequently called losartan, was patented in 1988, and, in 1991, its profile was published after the first studies on its effects in human volunteers and patients were published.

SECOND GENERATION ANGIOTENSIN II ANTAGONISTS

The considerable interest in developing improved angiotensin receptor blockers was due to their improved selectivity of action on the renin-angiotensin system compared with their predecessors—angiotensin-converting enzyme (ACE) inhibitors. It became clear that ACE inhibitors were unable to inhibit the generation of angiotensin peptides when they are formed in tissues by other enzymes, such as chymases.16 Furthermore, ACE inhibitors block the enzymes responsible for metabolizing bradykinin, so they enhance the endogenous levels of the angiotensin peptide. Losartan was marketed in 1994, and within 4 years, 13 other angiotensin II antagonists entered clinical trials and the first competitive compound to be marketed was Ciba-Geigy’s valsartan in 1996.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Binding to rat adrenal cortex microsomes</td>
<td>3H-angiotensin II Ki =16-30 nM</td>
</tr>
<tr>
<td>Specificity</td>
<td>No effect on contractile responses to acetyl choline, noradrenaline, renin, angiotensin-converting enzyme, bradykinin, histamine, or serotonin</td>
</tr>
<tr>
<td>Response to angiotensin II</td>
<td>Blocked vascular contractile responses</td>
</tr>
<tr>
<td>Adrenal release of aldosterone: no agonist effects (unlike saralasin)</td>
<td></td>
</tr>
<tr>
<td>Blood pressure in renal hypertensive rats</td>
<td>Reduced elevated blood pressure (ED50 parenteral 0.78mg/kg, 0.3mg/kg per os)</td>
</tr>
<tr>
<td>Efficacy equivalent to angiotensin-converting enzyme inhibitors</td>
<td></td>
</tr>
<tr>
<td>Heart rate or blood pressure in human volunteers</td>
<td>No effect11,12</td>
</tr>
</tbody>
</table>

Table I. Summary of the in vitro and in vivo pharmacological properties of losartan.
Compounds are structurally analogous to losartan, where 4 of them have the same biphenyl substitution attached to the acidic tetrasole contained in losartan. The affinity of these compounds for the angiotensin type 1 receptor, as measured by radioligand-binding techniques, varies between 7 to 9 pKi, with losartan being the lowest and irbesartan the highest. When the compounds are compared for antagonism of angiotensin II receptor-mediated contractility of vascular smooth muscle (rabbit aorta), the pA2 ranges from 7 to 10 for the 9 major compounds (Table II). While the pharmacological profiles of the above angiotensin receptor blockers all show potent antagonism of the actions of angiotensin II-mediated responses, the individual compounds differ in terms of in vitro and in vivo effects. All of the compounds lack effects on other G protein-mediated receptors. However, some of the angiotensin receptor blockers bind to peroxisome-proliferator-activated receptors (PPARs) (Figure 4). For example, irbesartan and telmisartan induce transcriptional activation of PPAR-γ, but eprosartan lacks this action. Losartan, telmisartan, and irbesartan have an effect on the PPAR-γ nuclear receptor with a potency equivalent to pioglitazone, which is an antidiabetic agent from the thiazolidinedione group. It remains to be established by appropriate clinical studies whether angiotensin receptor blockers with PPAR-γ properties lead to improved clinical outcomes compared with non-PPAR-γ angiotensin receptor blockers.

In high concentrations, some angiotensin receptor blockers can modify the function of potassium channels. While such effects could lead to QT prolongation, this has never been observed for any of the angiotensin receptor blockers in clinical studies.

### Table II. Comparison of the pharmacokinetic profiles of second-generation angiotensin II receptor blockers.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Oral dose (mg/day)</th>
<th>Prodrug</th>
<th>Half-life (hr)</th>
<th>Inverse agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>25-100</td>
<td>+</td>
<td>2.5</td>
<td>?</td>
</tr>
<tr>
<td>EXP3174</td>
<td></td>
<td>- Metabolite</td>
<td>6-9</td>
<td>+</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>400-800</td>
<td>--</td>
<td>5-9</td>
<td>N/A</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150-300</td>
<td>--</td>
<td>11-15</td>
<td>N/A</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>20-40</td>
<td>+</td>
<td>10-15</td>
<td>+</td>
</tr>
<tr>
<td>Telmesartan</td>
<td>40-80</td>
<td>--</td>
<td>24</td>
<td>+</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80-320</td>
<td>--</td>
<td>9</td>
<td>+</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4-12</td>
<td>+</td>
<td>9</td>
<td>?</td>
</tr>
</tbody>
</table>

All analogues are more than 90% bound to plasma proteins

A critical clinical aspect is the effect that modulation of the renin-angiotensin system has on long-term outcomes, including acute myocardial infarction, stroke, and overall mortality, both in diabetic and nondiabetic patients. A recent extensive meta-analysis comparing the effects of ACE inhibitors vs angiotensin receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in

### CLINICAL EFFICACY

Angiotensin receptor blockers are used extensively in the management of essential hypertension. They compare favorably with other classes of antihypertensive therapy. Many patients with diabetes also have hypertension. Some studies in diabetic patients suggest that modulating the actions of the renin-angiotensin system has a renoprotective effect.

![Figure 4. Angiotensin receptor blockers with a partial PPAR-γ agonistic effect may enhance PPAR-γ stimulation to inhibit AT1 receptor activity and activate the AT2 receptor.

**Abbreviations:** ARB, angiotensin receptor blocker; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; ERK, extracellular-signal-regulated kinase; NFkB, nuclear factor-κB; PPAR-γ, peroxisome-proliferator-activated receptor γ.

diabetic patients concluded that angiotensin receptor blocker treatment had no beneficial effect on these cardiovascular outcomes compared with placebo, while ACE inhibitors significantly reduced the incidence of these events. In summary, angiotensin receptor blockers had no significant effect on mortality, acute myocardial infarction, or heart failure hospitalization, whereas ACE inhibitors reduced all three of these parameters. This suggests that a highly specific blockade of the angiotensin II receptor does not have the expected benefit compared with ACE inhibitors. Angiotensin receptor blockers did, however, reduce the incidence of stroke in patients with essential hypertension.

The reason for these contrasting effects on outcomes between ACE inhibitors and angiotensin receptor blockers is not known, despite the widespread physiological role played by angiotensin II. Perhaps the non–angiotensin II off-target properties of ACE inhibitors play a role in the differing clinical outcomes.

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Understanding and Treating Heart Failure

Summaries of Ten Seminal Papers

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1. Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis
   R. A. Clark and others. BMJ. 2007

2. Advanced heart failure treated with continuous-flow left ventricular assist device

3. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study
   K. Swedberg and others. Lancet. 2010

4. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial
   W. T. Abraham and others. Lancet. 2011

5. Spironolactone for heart failure with preserved ejection fraction

6. Angiotensin–neprilysin inhibition versus enalapril in heart failure

7. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial
   S. A. Mortensen. JACC Heart Fail. 2014

8. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis
   D. Kotecha. Lancet. 2014

9. Adaptive servo-ventilation for central sleep apnea in systolic heart failure

10. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy

Selection of seminal papers by Ali Vazir, MB, BS, PhD, FRCP, FESC
National Heart and Lung Institute - Imperial College London - Institute of Cardiovascular Medicine and Science - Royal Brompton Hospital - UK

Highlights of the years by Sherri Smith, PhD
Publications office
Telemonitoring or structured telephone support programmes for patients with chronic heart failure: systematic review and meta-analysis

R. A. Clark, S. C. Inglis, F. A. McAlister, J. G. Cleland, S. Stewart

BMJ. 2007;334:942

In this study, the authors aimed to determine whether remote monitoring (ie, structured telephone support or telemonitoring) without regular clinic or home visits improves outcomes for patients with chronic heart failure. They looked at 15 electronic databases, hand searched previous studies, and made contact with authors and experts. Data was extracted by two investigators, who independently screened the results. They reviewed published randomized controlled trials comparing remote monitoring programs with usual care in patients with chronic heart failure managed within the community. They discovered 14 randomized controlled trials (4264 patients) on remote monitoring meeting the inclusion criteria, of which, 4 evaluated telemonitoring, 9 evaluated structured telephone support, and 1 evaluated both.

They found that remote monitoring programs reduced the rates of hospital admissions for chronic heart failure by 21% (95% CI, 11%-31%) and all-cause mortality by 20% (95% CI, 8%-31%). Of the 6 trials evaluating health-related quality of life, 3 reported significant benefits with remote monitoring, and, of the 4 studies examining health care costs with structured telephone support, 3 reported reduced cost and 1 reported no effect. The authors concluded that programs for chronic heart failure that include remote monitoring have a favorable effect on clinical outcomes in community-based patients with chronic heart failure.

In 2015, some of the authors of this publication performed a Cochrane systematic review, incorporating the latest trials of structured telephone support and noninvasive home telemonitoring. They included 41 studies, and, of these, 25 studies evaluated structured telephone support (9332 participants), 18 evaluated telemonitoring (3860 participants), and 2 included studies that compared both structured telephone support and telemonitoring with usual care.

In the Cochrane review, they found that noninvasive telemonitoring reduced all-cause mortality (risk ratio [RR], 0.80; 95% CI, 0.68-0.94; n, 3740; studies, 17; I²=24%; grade: moderate-quality evidence) and heart failure–related hospitalizations (RR, 0.71; 95% CI, 0.60-0.83; n, 2148; studies, 8; I²=20%; grade: moderate-quality evidence). Furthermore, structured telephone support also reduced all-cause mortality (RR, 0.87; 95% CI, 0.77-0.98; n, 9222; studies, 22; I²=0%; grade: moderate-quality evidence) and heart failure–related hospitalizations (RR, 0.85; 95% CI, 0.77-0.93; n, 7030; studies, 16; I²=27%; grade: moderate-quality evidence). These interventions also demonstrated improvements in health-related quality of life, heart failure knowledge, and self-care behaviors.

Therefore, there is compelling support for the use of structured telephone support and noninvasive home telemonitoring, as they reduced the risk of all-cause mortality and heart failure–related hospitalizations, and they improved health-related quality of life, heart failure knowledge, and self-care behaviors. Studies also demonstrated that participants were satisfied with the majority of these interventions.
Cardiac transplantation is the only definitive therapy for patients with advanced and medically refractory heart failure. However, cardiac transplantation is a suboptimal option in view of the large number of potential patients with advanced heart failure, the lack of donors, and the comorbidities that make most patients ineligible for cardiac transplantation. The concept of using a left ventricular assist device (LVAD) as a permanent solution for end-stage heart failure was tested in the landmark REMATCH randomized trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure) over a decade ago. In REMATCH, pulsatile-flow LVAD dramatically reduced mortality by 48% in 129 patients who had severe heart failure and who were not eligible for transplantation. In 2002, the FDA subsequently approved LVAD for destination therapy in the US. The 1-year and 2-year survival rates for pulsatile-flow LVAD were still suboptimal when compared with medical therapy for patients with advanced heart failure that were unsuitable for cardiac transplantation (52% vs 29% of the medically treated patients at year 1 and 23% vs 8% at year 2).

The aim of this study was to assess the efficacy and durability of newer and smaller LVADs with continuous-flow compared with pulsatile-flow LVADs. Enrolled patients with advanced heart failure who were ineligible for transplantation were randomized, in a 2:1 ratio, to undergo implantation of a continuous-flow device (134 patients) or the established and approved pulsatile-flow device (66 patients). The primary composite end point at 2 years was a survival free from a disabling stroke and reoperation to repair or replace the device. Secondary end points included survival, frequency of adverse events, quality of life, and functional capacity.

Preoperative characteristics were similar in the two treatment groups, with a median age of 64 years (range, 26-81), a mean left ventricular ejection fraction of 17%, and nearly 80% of patients were receiving intravenous inotropic agents. The primary composite end point was achieved in more patients with continuous-flow devices than with pulsatile-flow devices (62 of 134 [46%] vs 7 of 66 [11%]; P<0.001; hazard ratio, 0.38; 95% CI, 0.27-0.54; P<0.001), and patients with continuous-flow devices had superior actuarial survival rates at 2 years (58% vs 24%, P=0.008). Adverse events and device replacements were less frequent in patients with the continuous-flow device. The quality of life and functional capacity improved significantly in both groups. A limitation of the study was a lack of blinding, which may have influenced the reporting of adverse events and generally favored the continuous-flow pump.

The authors of the study concluded that treatment with a continuous-flow LVAD in patients with advanced heart failure significantly improved the probability of survival free from stroke and device failure at 2 years compared with a pulsatile-flow LVAD. Both devices significantly improved the quality of life and functional capacity. This study is an important step in LVAD technology and destination therapy, with a doubling in survival with newer continuous-flow pumps vs pulsatile-flow pumps (1 year increased to 2 years with continuous flow) and quadrupling survival when compared with inotropic therapy alone (6 months vs 2 years).
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

K. Swedberg, M. Komajda, M. Böhm, J. S. Borer, I. Ford, A. Dubost-Brama, G. Lerebours, L. Tavazzi; SHIFT Investigators

Lancet. 2010;376:875-885

Raised resting heart rate is a known risk factor for adverse outcomes in patients with heart failure and reduced ejection fraction (HFREF). This study aimed to assess the effect of heart-rate reduction by the If inhibitor ivabradine on outcomes in HFREF. Other than reducing heart rate, ivabradine has no other apparent direct cardiovascular effects.

The main eligibility criteria for the study included patients with symptomatic HFREF (New York Heart Association [NYHA] class II-IV, left ventricular ejection fraction [LVEF] ≤35%), who were in sinus rhythm with a heart rate ≥70 beats per min, a history of hospitalization for heart failure within the previous year, and on stable background treatment, including a β-blocker if tolerated. Patients were randomly assigned to either ivabradine or placebo in a double-blind fashion. The dose of ivabradine was titrated to a maximum of 7.5 mg twice daily. Patients and investigators were masked to treatment allocation. The primary end point was the composite of cardiovascular death or hospital admission for worsening heart failure. Analysis was by intention to treat.

In this study, 6558 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo). Of the 6558 patients, 84% were on diuretics, 22% on digoxin, 79% on an ACE inhibitor, 14% on an ARB, 90% on a β-blocker (26% were on a full-dose β-blocker), and 60% on an MRA. Data were available for analysis for 3241 patients in the ivabradine group and 3264 patients allocated to placebo. Patients were followed up for a median of 23 months.

The primary end point occurred in 793 (24%) patients in the ivabradine group and 937 (29%) in the placebo group (hazard ratio [HR], 0.82; 95% CI, 0.75-0.90; P<0.0001). The effects were driven mainly by hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR, 0.74; 95% CI, 0.66-0.83; P<0.0001) and deaths due to heart failure (151 [5%] vs 113 [3%]; HR, 0.74; 95% CI, 0.58-0.94, P=0.014). There were no significant reductions in all-cause or cardiovascular mortality. There was a consistent treatment effect in multiple prespecified sub-groups, but a diminishing benefit of ivabradine in patients with lower baseline heart rates (<77 beats per min). Subsequent reports suggested improvements in quality of life and LV systolic function.

Ivabradine was tolerated well, with fewer serious adverse events in the ivabradine group (3388 events) than in the placebo group (3847, P=0.025). However, 150 (5%) in the ivabradine group had symptomatic bradycardia compared with 32 (1%) in the placebo group (P<0.0001). Visual side effects (phosphenes) were reported by 89 (3%) patients on ivabradine and 17 (1%) on placebo (P<0.0001). In this study, only 3% of patients had implantable defibrillators and 1% had cardiac resynchronization therapy. This study supported the importance of reducing heart rate with ivabradine by showing an improvement in clinical outcomes in HFREF patients in sinus rhythm and confirmed the important role of heart rate in the pathophysiology of this disorder.

Following the results of the SHIFT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial), the 2012 ESC guidelines on the management of heart failure recommended the use of ivabradine for patients with HFREF in sinus rhythm and a heart rate >75 bpm on maximally tolerated doses of disease-modifying drugs for heart failure. Ivabradine could also be considered in patients with a contraindication to a β-blocker or with a β-blocker intolerance.
Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial


Lancet. 2011;377:658-666

Patients are usually admitted to the hospital for heart failure (HF) because of worsening signs and symptoms of congestion. Previous investigations have shown that increases in intracardiac and pulmonary artery pressures are the cause of this clinical congestion and are apparent several days to weeks before the onset of worsening signs, symptoms, and hospital admission, suggesting that early intervention targeting these pressures might reduce the risk of admission to the hospital. In a previous clinical trial, increases in intracardiac pressures often arose independently of weight changes, such that monitoring weight alone was inadequate to identify congestion in time to avert the events associated with HF. This observation might account for why telemonitoring systems that rely on patient-reported assessment of general health, symptoms of HF, and daily weight change have not reduced readmission or mortality rates.

In the CHAMPION trial (CardioMEMS Heart sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA class III heart failure patients), the hypothesis tested was that management of HF by using pulmonary artery pressures would greatly reduce the rate of HF-related hospitalizations. Patients with New York Heart Association (NYHA) class III HF, irrespective of the left ventricular ejection fraction, and a previous hospital admission for HF were enrolled in 64 centers in the US. A total of 550 patients underwent implantation of a wireless pulmonary artery hemodynamic monitor. These patients were then randomized to either management with a wireless implantable hemodynamic monitoring (W-IHM) system (ie, treatment group) or to a control group where information from the wireless device was not used. Patients were followed up for at least 6 months. Only patients were masked to their assignment group. In the treatment group, clinicians used daily measurements of pulmonary artery pressures in addition to standard care vs standard care alone in the control group. The primary efficacy end point was the rate of HF-related hospitalizations at 6 months. The safety end points assessed at 6 months were freedom from device-related or system-related complications (DSRRC) and freedom from pressure-sensor failures. All analyses were by intention to treat.

In 6 months, 84 HF–related hospitalizations were reported in the treatment group (n=270) compared with 120 in the control group (n=280, rate, 0.32 vs 0.44; hazard ratio [HR], 0.72, 95% CI, 0.60-0.85; P=0.0002). During the entire follow-up (mean, 15 months; SD, 7), the treatment group had a 37% reduction in HF–related hospitalizations compared with the control group (158 vs 254; HR, 0.63, 95% CI, 0.52-0.77, P<0.0001). A total of 8 patients had DSRRC; overall freedom from DSRRC was 98.6% (97.3-99.4) compared with a prespecified performance criterion of 80% (P<0.0001); and overall freedom from pressure-sensor failures was 100% (99.3-100.0).

The results of the CHAMPION study are consistent with, and extend, previous findings by definitively showing a significant and large reduction in hospitalization for patients with NYHA class III HF who were managed with a W-IHM system. The addition of information about pulmonary artery pressure to clinical signs and symptoms allows for improved HF management. Further technological advances will come with the increasing clinical use of these devices, which is likely to be the beginning of this revolution in patient monitoring that could reduce hospitalizations, be cost-effective, and may improve the patients’ experience.

Former Bosnian Serb Army commander Ratko Mladić, wanted for genocide, war crimes, and crimes against humanity, is arrested in Serbia; Tropical Storm Washi causes 1268 flash flood fatalities in the Philippines; and the Kepler space telescope discovers a solar system of six planets orbiting the star Kepler-11.
Mineralocorticoid receptor antagonists improve the prognosis for patients with heart failure (HF) and a reduced left ventricular ejection fraction. In this randomized, double-blind, placebo-controlled trial, the TOPCAT investigators (Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonisT) evaluated the effects of spironolactone in patients with HF and a preserved left ventricular ejection fraction (HFPEF).

The main eligibility criteria for the study were patients >50 years old, with the presence of HF symptoms (New York Heart Association class II-IV), LVEF ≥50%, and either a recent admission to the hospital within the last 12 months with HF being the major component of treatment or elevated brain natriuretic peptide (≥100 pg/mL) or elevated N-terminal pro–brain natriuretic peptide (level ≥360 pg/mL) within the last 60 days. Trial randomization was stratified according to whether patients were enrolled based on hospitalization or brain natriuretic peptide levels.

A total of 3445 patients were assigned to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF. Patients were followed up for a mean of 3.3 years, the primary outcome occurred in 320 of 1722 patients in the spironolactone group (18.6%) and 351 of 1723 patients in the placebo group (20.4%) (hazard ratio [HR], 0.89; 95% CI, 0.77-1.04; P=0.14). Of the components of the primary outcome, only hospitalization for HF had a significantly lower incidence in the spironolactone group than in the placebo group (206 patients [12.0%] vs 245 patients [14.2%]; HR, 0.83; 95% CI, 0.69-0.99; P=0.04). Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone. Treatment with spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia (18.7% vs 9.1% in the placebo group).

The overall findings of the study were that, in patients with HFPEF, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome. However, there was a nominally significant reduction in the secondary outcome of hospitalization for HF with spironolactone. Further reports from TOPCAT have shown that there were significant treatment differences based on how patients were recruited into the study. Spironolactone seemed to benefit patients enrolled in the natriuretic peptide stratum, but not those in the hospitalization stratum. Furthermore, the majority of these patients enrolled based on the hospitalization criterion (mainly from Russia and Georgia) had low event rates, which were similar to trials of hypertension as opposed to trials of HFPEF, and so patients were at a low risk for events. These reports showed that patients recruited from the Americas, who were enrolled mainly via the natriuretic peptide stratum, had significant improvements in the primary outcome.

Learning from TOPCAT, future trials of HFPEF are recommended to include a more precise definition of what is meant by hospitalization for HF and details of the admission could also be verified. Furthermore, TOPCAT emphasized the important role that the natriuretic peptide plays in the inclusion criterion of HF trials, particularly those on HFPEF, as they are powerful indicators of adverse events. Already, the Canadian Cardiac Society has endorsed spironolactone as a consideration for patients with HFPEF and elevated natriuretic peptides.
Angiotensin–neprilysin inhibition versus enalapril in heart failure


This publication introduces a new class of drug referred to as angiotensin receptor–neprilysin inhibitors (ARNI). LCZ696 is a combination of the angiotensin receptor blocker valsartan and the neprilysin inhibitor sacubitril. Neprilysin inhibition blocks the degradation of neuroendopeptidases, leading to an accumulation of endogenous neuropetides that have vasodilator and likely antioxidant properties. It also leads to the accumulation of other peptides, such as bradykinin, adrenomedullin, substance P, and calcitonin gene–related peptide (other powerful vasodilators).

The PARADIGM-HF investigators (Prospective comparison of Angiotensin Receptor–neprilysin inhibitor with an Angiotensin-converting enzyme inhibitor to Determine Impact on Global mortality and Morbidity in Heart Failure trial) aimed to assess the effectiveness of LCZ696 vs an established treatment with the angiotensin-converting enzyme (ACE) inhibitor, enalapril. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure (HF), but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

Randomization followed a run-in period where patients had to tolerate either LCZ696 200 mg twice daily or enalapril 10 mg twice daily. Approximately 10,521 patients entered the run-in period. Of these patients, 2079 did not fulfill the criteria for randomization. A total of 8442 patients with New York Heart Association class II, III, or IV HF and an ejection fraction ≤40% were randomized in a double-blind manner to receive guideline-recommended therapy plus either LCZ696 200 mg twice daily or enalapril 10 mg twice daily.

The trial was stopped early, according to prespecified rules, after a median 27-month follow-up, because the boundary for an overwhelming benefit with LCZ696 was crossed. A total of 558 (13.3%) and 693 (16.5%) patients, respectively, died from cardiovascular causes (HR, 0.80; 95% CI, 0.71-0.89; P<0.001). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for HF by 21% (P<0.001) and decreased the symptoms and physical limitations of HF (P=0.001). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema, but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

A criticism of the study is that enalapril at a dose of 10 mg twice daily, where the maximum dose is 20 mg twice daily, was compared with LCZ696 at dose of 200 mg twice daily. The rationale for using this ACE inhibitor and this dose were the fact that enalapril is the only ACE inhibitor shown to reduce mortality in chronic heart failure and the average dose achieved in PARADIGM-HF was greater than that used in either the CONSENSUS (COoperative North Scandinavian Enalapril Survival Study) or SOLVD (Studies Of Left Ventricular Dysfunction) studies.

In summary, this new class of drug is likely to replace the use of ACE inhibitors as the cornerstone of therapy for heart failure due to its overwhelming results. However, its endorsement to date has been slow by the clinical community, probably due to a combination of issues related to cost and slow uptake by guideline committees and prescribers.

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An estimated 276 girls and women are abducted and held hostage from a school in Nigeria; Burkina Faso President Blaise Compaoré resigns after widespread protests in response to the attempt to abolish presidential term limits; and Miklós Jancsó, a Hungarian film director and screenwriter, dies at age 92.
Heart failure (HF) is an energy-depleted state associated with low myocardial adenosine triphosphate (ATP) production, mitochondrial dysfunction, abnormal calcium handling, increased reactive oxygen species generation, and endothelial dysfunction. Coenzyme Q10 (CoQ10) has a critical role in ATP production, is a potent anti-inflammatory agent, and it may improve endothelial function. Lower CoQ10 levels are seen in patients with advanced HF symptoms and with lower ejection fractions. In several small studies, CoQ10 was shown to have little or no benefit with respect to improving outcomes. However, the large prospective, randomized, double-blind, placebo-controlled, multicenter trial Q-SYMBO (coenzyme Q10 as adjunctive treatment for chronic HF focusing on changes in symptoms, Blomarker status, and long-term Outcome) has shown promise for CoQ10 as a potential therapeutic option for HF.

In Q-SYMBO, 420 patients with heart failure and reduced systolic function with New York Heart Association class III-IV were randomized to standard therapy and either CoQ10 (n=202) given as 100 mg thrice daily or placebo (n=218). The primary short-term end points at 16 weeks were changes in NYHA functional classification, 6-min walk test, and levels of N-terminal pro-B-type natriuretic peptide. The primary long-term end point at 2 years was the composite of major adverse cardiovascular events as determined by a time to first event analysis.

This trial showed that there were no significant changes in the short-term end points; however, the primary long-term end point was reached by 15% (30 events) of patients in the CoQ10 group vs 26% (57 events) in the placebo group (hazard ratio [HR], 0.50; 95% CI, 0.32-0.80; P=0.003). Furthermore, the CoQ10 group had lower cardiovascular mortality (9% vs 16%; P=0.026), all-cause mortality (10% vs 18%; P=0.018), and incidence of hospital stays for HF (P=0.033). A significant improvement in the NYHA class was observed in the CoQ10 group after 2 years (P=0.028).

The results of this trial have renewed interest in the use of CoQ10 for HF. A limitation of the study included the extended time period that was required to fulfill recruitment (>8 years) in more than 17 centers and 9 countries. The reasoning for the extended time required to complete study enrollment is attributed to the combination of the nonpatentable feature of CoQ10 and a low budget for the study that had to compete with drug company-sponsored studies.

In summary, Q-SYMBO showed that treating chronic HF patients with CoQ10 was safe and it improved symptoms and reduced major adverse cardiovascular events, but this study was of moderate size. However, future adequately powered studies are merited to evaluate the clinical benefit in patients with HFREF sufficiently. Furthermore, the rationale for the use of CoQ10 in HEPEF is merited and a well-conducted randomized controlled trial will be required to demonstrate efficacy and safety in this population.
Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis


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The use of β-blockers for patients with chronic heart failure with reduced ejection fraction (HFREF) was instituted after a series of mechanistic studies and large randomized controlled trials that showed a significant reduction in the rates of morbidity and mortality. International guidelines recommend the use of β-blockers in symptomatic patients with HFREF, and this has had a class 1A recommendation. Atrial fibrillation and heart failure often coexist, causing substantial cardiovascular morbidity and mortality. β-Blockers are indicated in patients with symptomatic HFREF; however, the efficacy of these drugs in patients with concomitant atrial fibrillation is uncertain.

In this meta-analysis, authors used individual-patient data to assess the efficacy of β-blockers in patients with heart failure and sinus rhythm compared with atrial fibrillation. They extracted individual patient data from 10 randomized controlled trials comparing β-blockers with placebo in heart failure. The presence of sinus rhythm or atrial fibrillation was ascertained from the baseline electrocardiograph. The primary outcome of the study was all-cause mortality and the analysis was performed by intention to treat. Outcome data were meta-analyzed with an adjusted Cox proportional hazards regression.

They used data from 18,254 patients, and, of these, 13,946 (76%) had sinus rhythm and 3,066 (17%) had atrial fibrillation at baseline and the remainder had other rhythms, such as paced beats or heart block. Crude death rates over a mean follow-up of 1.5 years (SD, 1.1) were 16% (2,237 of 13,945) in patients with sinus rhythm and 21% (633 of 3,064) in patients with atrial fibrillation. β-Blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (hazard ratio [HR], 0.73; 95% CI, 0.67-0.80; \( P<0.001 \)), but not in patients with atrial fibrillation (HR, 0.97; 95% CI, 0.83-1.14; \( P=0.73 \)), with a significant \( P \) value for interaction of baseline rhythm (\( P=0.002 \)). The lack of efficacy for the primary outcome was noted in all subgroups of atrial fibrillation, including age, sex, left ventricular ejection fraction, New York Heart Association class, heart rate, and baseline medical therapy.

The authors concluded that, based on these results, β-blockers should not be used preferentially over other heart rate-control medications and should not be regarded as standard therapy to improve prognosis in patients with concomitant HFREF and atrial fibrillation. However, based on this study, one should not change clinical practice, as there is no clear explanation of these findings and using β-blockers does not appear to be harmful as is reflected in this study. Taking a closer look at this data, one finds that patients with atrial fibrillation were different from patients in sinus rhythm, for example, atrial fibrillation patients were older, more likely to be men, had worse symptoms, and were commonly treated with a combination of digoxin and amiodarone, which could interact with β-blockers. Other explanations include potential impact of unmeasured confounding factors, such as a conduction-system disease (eg, pauses or pacemaker use) or potential differential responses in patients with milder symptoms vs those with a more advanced disease. These potential explanations require further exploration.

Massimo Tamburini, an Italian motorcycle designer for Cagiva, Ducati, and MV Agusta, dies at age 70 from lung cancer; the Swedish princess Leonore, Duchess of Gotland is born; and Prince Harry launches the Invictus Games, a Paralympic-style sporting championship for wounded soldiers
Central sleep apnea (CSA) is characterized by cycles of apnea and hyperpnea during sleep due to abnormalities in regulation of breathing within respiratory centers in the brainstem. CSA is common in patients with heart failure (HF), with a 20% to 45% prevalence rate, and its presence is reported to be a marker of HF severity. It is also described in some studies to be independently associated with increased morbidity and mortality in patients with HF.

Adaptive servo-ventilation (ASV) is a form of positive pressure ventilation with a variable pressure algorithm that delivers back-up breaths and high pressure during apnea and lower pressure during hyperpnea, resulting in resolution of the apnea-hypopnea index (AHI) to normal levels in most cases. ASV treats CSA more effectively than other forms of positive pressure, such as continuous positive airway pressure (CPAP).

The SERVE-HF trial (treatment of Sleep-disordered breathing with predominant central sleep apnea by adaptive servo-ventilation in patients with HF) investigated the effects of adding ASV (AutoSet CS, ResMed) to guideline-based medical treatment on survival and cardiovascular outcomes in patients who had HF with reduced ejection fraction and predominantly CSA. This was a time-to-event analysis with the primary outcome being the first event of death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening heart failure. In SERVE-HF, 1325 were randomized to ASV or optimal medical therapy with a median 31-month follow-up duration (range, 0 to 80).

This trial unexpectedly demonstrated that, despite effectively treating CSA (AHI dropped from 31.2 per hour at baseline to 6.6 per hour at 12 months), ASV had no impact on the primary end point of the trial (54.1% and 50.8%, respectively; hazard ratio [HR], 1.13; 95% CI, 0.97-1.31; P=0.10). Surprisingly, ASV was associated with harm as there was an increase in all-cause mortality (HR, 1.28; 95% CI, 1.06-1.55; P=0.01) driven by an increased risk of cardiovascular death (HR, 1.34; 95% CI, 1.06-1.55; P=0.006). The increase in cardiovascular death was also driven mainly by an increase in sudden cardiac death (the mechanism by which sudden cardiac death occurred is unclear; therefore further analysis from SERVE-HF is eagerly awaited.

In contrast with the findings of smaller studies and the meta-analyses that showed improvements in surrogate markers, such as brain natriuretic peptide, left ventricular ejection fraction, and quality of life scores with ASV in patients with HFREF and CSA, the results of SERVE-HF were surprising and have now generated further controversy in the way CSA is viewed, such that the presence of CSA may be viewed as a compensatory mechanism in HF, which may have favorable effects, and perhaps treating it may not be beneficial. For example, the presence of hyperpnea following an apnea may lead to improved lung expansion, recruitment of collapsed alveoli in a congested lung, and improved oxygenation. However, further studies are required to explore this hypothesis.

Adaptive servo-ventilation for central sleep apnea in systolic heart failure


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Hitoshi Saito, a Japanese judoka who won two consecutive gold medals at the Olympic games, dies at age 54 from cholangiocarcinoma; Princess Charlotte of Cambridge, daughter of Prince William, Duke of Cambridge, is born; and Hurricane Patricia becomes the most intense hurricane ever recorded in the Western Hemisphere, with winds of 345 km/hour and a pressure of 879 mbar.
Coronary-artery bypass surgery in patients with ischemic cardiomyopathy


The STICH study (Surgical Treatment for Ischemic Heart Failure) consisted of two components—a surgical revascularization component and a surgical ventricular reconstruction component. The surgical revascularization component was designed to test the hypothesis that coronary artery bypass grafting (CABG) plus guideline-directed medical therapy for coronary artery disease, heart failure (HF), and left ventricular dysfunction would improve survival over that with medical therapy alone. In the analysis of data from the surgical revascularization component at a median follow-up of 56 months, no significant difference in the rate of all-cause mortality between the CABG group and the medical-therapy group was observed, although the rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes were lower among patients in the CABG group. In the present study, the authors report the results of the STICH Extension Study (STICHES), which was conducted to evaluate the long-term, 10-year effects of CABG in patients with ischemic cardiomyopathy.

A total of 1212 patients with an ejection fraction ≤35% and coronary artery disease amenable to CABG were randomly assigned to undergo CABG plus medical therapy (CABG group, 610 patients) or medical therapy alone (medical-therapy group, 602 patients). The primary outcome was death from any cause. Major secondary outcomes included death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes. The median duration of follow-up, including the current extended follow-up study, was 9.8 years.

A primary outcome event occurred in 359 patients (58.9%) in the CABG group and 398 patients (66.1%) in the medical-therapy group (hazard ratio [HR] with CABG vs medical therapy, 0.84; 95% CI, 0.73-0.97; P=0.02 by log-rank test). A total of 247 patients (40.5%) in the CABG group and 297 patients (49.3%) in the medical-therapy group died from cardiovascular causes (HR, 0.79; 95% CI, 0.66-0.93; P=0.006 by log-rank test). Death from any cause or hospitalization for cardiovascular causes occurred in 467 patients (76.6%) in the CABG group and in 524 patients (87.0%) in the medical-therapy group (HR, 0.72; 95% CI, 0.64-0.82; P<0.001 by log-rank test).

Thus, patients with ischemic cardiomyopathy who underwent surgical revascularization and medical therapy had better long-term outcomes than those who were treated with medical therapy alone, with the occurrence of lower rates of death from any cause, death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes over 10 years. A possible explanation for the results include the fact that the majority of patients randomly assigned to undergo CABG received a left internal mammary artery (LIMA) graft (91.1%) vs 9.9% of patients in the earlier trials of CABG.

In summary, the results of the STICHES study support a significant benefit of CABG plus medical therapy over medical therapy alone with respect to the rate of death from any cause among patients with ischemic cardiomyopathy. It is not known whether percutaneous coronary revascularization vs medical therapy alone would result in benefits similar to those that were observed with CABG, and future studies are required to address this question.

David Bowie, an English singer, songwriter, actor, and record producer, dies at age 69 from liver cancer; Joaquín Guzmán, widely regarded as the world’s most powerful drug trafficker, is recaptured following his escape from a maximum security prison; and the World Health Organization announces an outbreak of the Zika virus.
Understanding and Treating Heart Failure

Bibliography of One Hundred Key Papers

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