A practical guide to chronic heart failure management

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Despite significant recent advances, heart failure remains a challenging condition to both diagnose and treat. This article discusses the recommended investigations to aid diagnosis and the role of pharmacotherapy in the management of chronic heart failure.

Chronic heart failure is a major global health problem. Approximately 2% of adults in developed countries are affected, with this figure rising to around 7–10% in older adults. This prevalence is expected to increase over the coming decades due to the combination of an ageing population and declining fatality rates in other cardiovascular diseases that predispose to the development of heart failure. However, developments in the evidence-based treatment of heart failure over the past 30 years have resulted in significant reductions in patient morbidity and mortality. With such an array of therapies now available, this review provides an overview of the management of chronic heart failure, focusing on key pharmacological therapies and significant recent developments in this area.

Diagnosis of chronic heart failure
Classical symptoms and signs of heart failure – such as exertional dyspnoea, orthopnoea and peripheral oedema – have poor sensitivity and specificity and should not be relied upon alone to make a diagnosis of heart failure. Thus, objective evidence of myocardial dysfunction must be demonstrated for a diagnosis. Echocardiography is the first-line investigation to identify myocardial dysfunction, with other imaging modalities such as cardiac magnetic resonance (CMR) imaging reserved for selected patients.

Using echocardiography, it is usually possible to classify left ventricular function – from preserved systolic function through to severe impairment. The calculation of a left ventricular ejection fraction (LVEF) can augment this classification. Current therapies are only proven effective for those patients with heart failure with reduced ejection fraction (HFrEF).

The diagnosis of heart failure with preserved ejection fraction (HFpEF) is more challenging and is reliant on several echocardiographic markers of impaired diastolic function. Often, patients have a mild degree of concurrent systolic dysfunction. Unfortunately, there are currently no pharmacological treatments that improve mortality or reduce admissions in patients with HFpEF.
Cardiac biomarkers also play an important role in the diagnosis of heart failure, particularly in primary care. Natriuretic peptides, such as B-type natriuretic peptide (BNP) or the inactive fragment N-terminal pro-B-type natriuretic peptide (NT-proBNP), are neurohormonal peptides that are released from stretched myocardial muscle. The main utility of natriuretic peptides lies in their negative predictive value, such that they are recommended for ruling out a diagnosis of heart failure, although natriuretic peptides also hold powerful prognostic value. Elevated concentrations should not be used in isolation to establish a diagnosis of heart failure but can help to identify patients in whom investigation with echocardiography would be useful. In the non-acute setting, the concentrations at which international guidelines consider a diagnosis of heart failure to be unlikely are NT-proBNP <125pg/ml and BNP <35pg/ml.

Interpretation of natriuretic peptide concentrations can be complicated by co-morbid medical conditions. Atrial fibrillation, advanced age and renal failure can increase natriuretic peptide concentrations, whereas obesity can lower them. Treatment with sacubitril-valsartan (Entresto), which is discussed later in this article, increases BNP (a reflection of its therapeutic effect) but lowers NT-proBNP concentrations in a patient with established heart failure (reflecting an improved prognosis). As a result, NT-proBNP is the only natriuretic peptide measurement recommended in the 2018 NICE heart failure guidance (see Figure 1).

Improving cardiovascular outcomes with pharmacotherapy

The over-activation of both the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system are central to the progressive worsening in HFrEF patients over time. Attenuation of these pathways underpins HFrEF management (see Figure 2), with neurohormonal antagonists shown in many large clinical trials to reduce mortality and morbidity in these patients.

All patients with HFrEF should be prescribed an angiotensin-converting enzyme (ACE) inhibitor (for inhibition of the RAAS system), and a beta-blocker such as carvedilol or bisoprolol to combat the sympathetic nervous system (see Figure 3). In patients with severe left ventricular systolic dysfunction (LVEF ≤35%), further attenuation of the RAAS pathway using a mineralocorticoid-receptor antagonist (MRA) – eplerenone

Figure 1. Summary of the recommendations on tests to offer to diagnose chronic heart failure from NICE's guideline on chronic heart failure in adults
and spironolactone being the two evidence-based drugs in this class – can further reduce heart failure hospitalisations and all-cause mortality. Where an ACE inhibitor is not tolerated, an angiotensin II-receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI – see below) can be used instead. Each of these medications should be titrated to the maximum tolerated dose, with regular monitoring of serum electrolytes on initiation of ACE inhibitors, ARBs or MRAs. Recommendations for the management and monitoring of ACE inhibitors, beta-blockers and MRAs in heart failure are outlined in practical guidance published by McMurray et al. in the European Journal of Heart Failure.

**Angiotensin receptor-neprilysin inhibitors**

Although clinical outcomes for patients with heart failure have improved dramatically over the past 30 years, there is still a 7–17% mortality at one-year post-diagnosis. Most of these deaths are due to worsening heart failure or sudden cardiac death.

Sacubitril-valsartan, a first-in-class ARNI, has recently been shown to confer significant additional benefits in HFrEF when compared to the ACE inhibitor enalapril. In the PARADIGM-HF trial, treatment with sacubitril-valsartan reduced cardiovascular mortality by 20% and heart failure hospitalisation by 21% in patients with HFrEF. Patients treated with sacubitril-valsartan also had a 16% lower all-cause mortality and 20% reduction in sudden death. They were also significantly less likely to have worsening of their symptoms. These benefits are particularly impressive as sacubitril-valsartan was compared with enalapril – our gold-standard heart failure therapy for 30 years – and not a placebo.

ARNIs such as sacubitril-valsartan work through their modulation of natriuretic peptides, such as BNP (see Figure 4). These peptides form part of an endogenous cardioprotective mechanism against myocardial stress: helping to stimulate diuresis, reduce cardiac hypertrophy and promote vasodilatation through their inhibition of neurohormonal activation of the RAAS and sympathetic nervous system. Neprilysin is the enzyme that would naturally break down cardioprotective peptides such as BNP. The pro-drug sacubitril inhibits the neprilysin enzyme and so raises the concentrations of natriuretic peptides, prolonging their cardioprotective effect.

NICE currently recommends sacubitril-valsartan as a second-line treatment in patients with HFrEF (LVEF ≤35%) who remain symptomatic despite optimal therapy with an ACE inhibitor or ARB. In Scotland, SIGN has a similar stance except with a LVEF ≤40%. Sacubitril-valsartan is commenced in place of, rather than in addition to, a patient’s existing ACE inhibitor or ARB.

When initiating sacubitril-valsartan, patients should stop their ACE inhibitor at least 36 hours before the first dose, to avoid the risk of angioedema if the two drugs are used con-jointly. The standard starting dose is typically 49/51mg twice daily, uptitrating to 97/103mg twice daily after two to four
For those with a systolic blood pressure of 90–100mmHg, the lower starting dose of 24/26mg twice daily is recommended instead. It may be possible to reduce the dose of loop or thiazide diuretic because of the additional diuretic effect of sacubitril-valsartan. As with ACE inhibitors and ARBs, serum electrolytes and renal function should be monitored regularly.

Symptomatic management in chronic heart failure
Management of heart failure symptoms can be challenging and initiation of therapies that reduce mortality may have little effect on the way a patient feels – at least initially. Although having no known effect on mortality or rates of rehospitalisation for heart failure, loop diuretics can relieve dyspnoea associated with pulmonary congestion, and the discomfort from peripheral oedema. They are recommended in patients with heart failure regardless of LVEF. Heart failure with reduced ejection fraction, fluid restriction to 1500–2000ml per day can also help control symptoms. Patients should be encouraged to monitor their weight daily to detect early deviations from their ‘dry weight’ and avoid acute decompensated episodes. Selected patients may be able to tailor diuretic therapy as part of a self-care regimen.

Other drug therapies in advanced heart failure
Higher resting heart rates in sinus rhythm are associated with adverse outcomes in heart failure. However, this is not a com-
mon finding in ambulant heart failure patients who are receiving guideline-recommended doses of beta-blocker. The SHIFT study investigated patients with a LVEF ≤35% who were in sinus rhythm >70bpm despite optimal first-line therapy. Although there was no effect on mortality, ivabradine reduced heart failure hospitalisation by 26%.9 

Digoxin is an alternative strategy for severe unremitting symptoms despite optimal medical therapy. For those in sinus rhythm, digoxin may improve heart failure symptoms and prevent deterioration leading to hospital admission – although this finding was shown prior to currently available disease-modifying therapies.10 Furthermore, similarly to ivabradine, digoxin was not shown to reduce mortality. However, digoxin can also be used for additional rate control in atrial fibrillation if this is necessary despite optimal doses of beta-blocker, whereas ivabradine has no clinically useful action in patients with atrial fibrillation.

The role of hydralazine and nitrates
In selected patients with unremitting heart failure symptoms, vasodilation with the combination of hydralazine and isosorbide dinitrate (H-ISDN) can improve cardiovascular outcomes and reduce mortality. ISDN increases the intracellular concentration of soluble guanylate cyclase and cyclic GMP – both of which can contribute to myocardial dysfunction and heart failure progression if their concentrations fall.11,12

Data from the A-HeFT trial found that the addition of H-ISDN to standard heart failure treatment (including ACE inhibitors, beta-blockers and MRA), specifically in African American patients with symptomatic HFrEF, reduced mortality and rates of heart failure hospitalisation compared to standard therapy.13 Current guidelines therefore recommend the addition of H-ISDN in Black patients with severe heart failure (LVEF ≤35%, or with a LVEF <45% combined with a dilated left ventricle) who remain symptomatic despite treatment with an ACE inhibitor, beta-blocker and an MRA.

The results of A-HeFT are difficult to translate to other ethnic groups, but one small randomised controlled trial, conducted prior to the advent of ACE inhibitors, did show a borderline reduction in mortality in men of all ethnicities treated with H-ISDN.14 This was compared to controls receiving only digoxin and diuretics, with neither group receiving beta-blockers. Although evidence is limited, H-ISDN can be used to reduce mortality in symptomatic heart failure patients who cannot tolerate either ACE inhibitors or ARBs (for example, due to hyperkalaemia or renal dysfunction). Typical side-effects reported with H-ISDN include headache, dizziness and nausea.

Thromboembolic risk and coronary artery disease in heart failure
For patients with heart failure and sinus rhythm, there are no data to support the routine use of aspirin,1 or anticoagulation with either warfarin or a direct oral anticoagulant (DOAC). The recently published COMMANDER-HF trial found no improvement in the composite primary efficacy outcome of death from any cause, myocardial infarction or stroke with the DOAC rivaroxaban compared to placebo in patients with chronic heart failure.

**Figure 4.** Mode of action of the angiotensin receptor-neprilysin inhibitor sacubitril-valsartan

<table>
<thead>
<tr>
<th>Natriuretic peptide system</th>
<th>Renin-angiotensin-aldosterone system</th>
</tr>
</thead>
<tbody>
<tr>
<td>pro-BNP</td>
<td>AT1 receptor</td>
</tr>
<tr>
<td>BNP</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>↑ Blood pressure</td>
</tr>
<tr>
<td>↓ Blood pressure</td>
<td>↑ Sympathetic tone</td>
</tr>
<tr>
<td>↓ Sympathetic tone</td>
<td>↑ Aldosterone levels</td>
</tr>
<tr>
<td>↓ Aldosterone levels</td>
<td>↑ Fibrosis</td>
</tr>
<tr>
<td>↓ Fibrosis</td>
<td>↑ Hypertrophy</td>
</tr>
<tr>
<td>↓ Hypertrophy</td>
<td>Sodium retention</td>
</tr>
<tr>
<td>Natriuresis</td>
<td>Water retention</td>
</tr>
<tr>
<td>Diuresis</td>
<td></td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; AT1 receptor = angiotensin II type 1 receptor
heart failure, coronary artery disease and sinus rhythm.\textsuperscript{15} Although anticoagulation with warfarin can reduce the risk of stroke in heart failure, any benefit is outweighed by a significantly increased risk of major haemorrhage.\textsuperscript{16,17} In patients with heart failure and atrial fibrillation, anticoagulation is still recommended due to the increased risk of thromboembolic events such as stroke, and the \textit{CHA}_{2}\textit{DS}_{2}-\textit{VASc} and HAS-BLED scores should be used to determine the likely risk-benefit ratio.

There is also no benefit to the routine use of statins in heart failure patients with or without coronary artery disease.\textsuperscript{18,19} In patients with known coronary artery disease who are already taking a statin, continuation of therapy is advised.\textsuperscript{1,20}

### Iron deficiency and anaemia in heart failure

In patients with heart failure, iron deficiency is associated with lower health-related quality of life and predicts worse clinical outcomes.\textsuperscript{21} Two large meta-analyses have reported that intravenous (IV) iron can confer benefit in selected heart failure patients who remain symptomatic despite other medical therapies.\textsuperscript{17,22} The CONFIRM-HF trial in patients with iron deficiency (with or without anaemia) found that IV ferric carboxymaltose (FCM) improved exercise ability and reduced the rate of heart failure-specific hospitalisation compared to placebo.\textsuperscript{23} Although current European guidelines already suggest that IV FCM should be considered in symptomatic HFrEF patients with iron deficiency,\textsuperscript{1} there are several large studies ongoing to assess whether IV iron also reduces mortality.

### Future of pharmacotherapy in heart failure

#### Sodium-glucose co-transporter 2 inhibitors

The EMPA-REG trial, which assessed the role of the sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin in diabetic patients, found significant reductions in heart failure admissions and cardiovascular death in patients allocated to treatment with empagliflozin.\textsuperscript{24} This benefit was consistent in patients both with and without baseline heart failure. The mechanism for this is not fully established (and is likely multifactorial); however, the diuretic effect may play a role. As the EMPA-REG trial was not specifically designed to assess empagliflozin in patients with heart failure, there are now several ongoing trials of SGLT2 inhibitors in patients with HFrEF and HFpEF, both with and without diabetes.

#### Guanylate cyclase stimulation

A reduction in intracellular concentrations of guanylate cyclase and cyclic GMP can contribute to progressive myocardial dysfunction in heart failure and this has been a therapeutic target for decades with H-ISDN. More recently, the SOCRATES-REDUCED trial investigated the role of direct guanylate cyclase stimulation with the novel agent, vericiguat. Although this phase 2 clinical trial was not powered for clinical outcomes, exploratory analysis of the data has suggested trends towards improvements in cardiovascular death, heart failure hospitalisation and LVEF in patients treated with vericiguat.\textsuperscript{25} There are also some emerging data that vericiguat improves quality of life in patients with HFpEF – for which no effective therapies

### Table 1. Drug classes that may exacerbate symptoms and deterioration in established chronic heart failure

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Examples</th>
<th>Sodium and water retention</th>
<th>Neuro-hormonal activation</th>
<th>Reduced contractility</th>
<th>Pro-arrhythmic</th>
<th>Increased cardiac demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone, rosiglitazone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Prednisolone, hydrocortisone, fluocortisone</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ibuprofen, coxibs, diclofenac, etodolac, indometacin</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Non-dihydropyridine calcium-channel blockers</td>
<td>Verapamil, diltiazem</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCAs)</td>
<td>Amitriptyline, doxepine, nortriptyline, imipramine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Over-the-counter medication</td>
<td>Decongestants (pseudoephedrine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

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Cardiac myosin activators
Omecamtiv mecarbil is a first-in-class cardiac myosin activator that increases the entry force of myosin into the tightly bound force-producing state with actin. This increases the duration of systole and increases stroke volume without an increase in myocyte calcium. Two small studies of omecamtiv mecarbil in acute and chronic heart failure have demonstrated improvements in both systolic ejection time and left ventricular end-systolic diameters compared to placebo.27,28 There was also a significant reduction in NT-proBNP concentration in patients treated with omecamtiv mecarbil, suggesting an improved prognosis.27 This is currently the focus of a large mortality trial in chronic heart failure (GALACTIC-HF; ClinicalTrials.gov Identifier: NCT02929329).

Drugs to avoid in heart failure
Many drugs can aggravate established heart failure and in some circumstances are contraindicated (see Table 1). Other therapies such as tumour necrosis factor (TNF) inhibitors (eg etanercept) and some anti-cancer agents (eg trastuzumab, anthracyclines) can themselves lead to the development of heart failure.

Role of multidisciplinary teams in chronic heart failure management
From initial diagnosis through to supportive care for end-stage heart failure, a multidisciplinary team (MDT) approach is considered the gold-standard model for the delivery of heart failure care. This approach has been shown to reduce both all-cause mortality and heart failure-associated hospitalisations, as well as improve patients’ quality of life, when compared to standard care.29,30 Dedicated heart failure pharmacist-led clinics, for example, have been shown to increase the number of patients receiving evidence-based pharmacotherapy compared to standard follow-up, with those attending these clinics also receiving medication dosages closer to the guideline-based targets.31

Device therapy in advanced heart failure
Sudden cardiac death due to ventricular arrhythmia is thought to be a common cause of death in heart failure. Although neurohormonal antagonists (ACE inhibitors, beta-blockers, MRAs and sacubitril-valsartan) have been shown to reduce sudden cardiac death, they cannot terminate ventricular arrhythmias if they do develop. Implantable cardioverter defibrillators (ICDs) are designed to abort malignant ventricular arrhythmias and are indicated for either primary prevention of sudden cardiac death in individuals felt to be at high risk, or as a secondary prevention measure for those who have survived symptomatic ventricular arrhythmia.1

In many cases of heart failure with severely reduced ejection fraction, there is associated electrical dyssynchrony (characterised on ECG by prolongation of the QRS complex or a bundle-branch block). For these patients, electrical resynchronisation using cardiac resynchronisation therapy (also known as biventricular pacing) can reduce both mortality and rehospitalisation rates, as well as improve symptoms and exercise capacity.1 Cardiac resynchronisation therapy may be beneficial in patients with severe symptoms whereas defibrillators, in general, are not. The role of devices in advanced heart failure is an expanding field.

Surgical options in chronic heart failure
In highly selected heart failure patients, heart transplantation may be necessary, although the availability of suitable donor organs is a major hurdle. Mechanical cardiac support with long-term left ventricular assist devices (LVADs) is increasingly being used as an alternative option in some patients. However, these are only available to patients as a bridge to heart transplantation. Although currently small numbers are implanted, this is likely to increase over the coming decades with improvements in design, reduced cost and better long-term outcomes.

Repair of the mitral valve can also benefit some heart failure patients where progressive dilation and remodelling of the left ventricle has caused secondary mitral regurgitation. While there are some conflicting reports, interventional percutaneous edge-to-edge repair of the mitral valve (MitraClip) has been shown in a number of studies to improve quality of life, left ventricular volumes and possibly reduce mortality, and so should be considered in those with severe secondary mitral regurgitation.32,33 There are less data to support surgical repair for mitral regurgitation.34

Conclusion
Despite significant advances over the past three decades, heart failure remains a challenging condition to both diagnose and treat. Neurohormonal antagonists remain central to the management of HFrEF, reducing mortality and improving symptoms, and should be up-titrated to target dosages as far as tolerated. Sacubitril-valsartan is a major step forward and a significant recent addition to the therapeutic options available. It is important that unfamiliarity with this drug is addressed so that it is prescribed appropriately.

The role of devices in heart failure is evolving, and both primary and secondary care clinicians should be aware of the benefits these treatment strategies deliver. Working alongside patients, a multidisciplinary team is of paramount importance to ensure that the complex care needs are met for this growing, multi-morbid and ageing population.

References


**Declaration of interests**

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