# Evidence-based drug therapy in the management of heart failure

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## Educational aims

- To provide an update of the most recent guideline recommendations for the pharmacotherapeutic management of heart failure.
- To distinguish between those drugs which offer symptomatic relief and those which offer prognostic benefit.
- To highlight the monitoring requirements associated with the drugs used.

## Key words

heart failure, angiotensin-converting enzyme inhibitors, beta-blockers, loop diuretics, aldosterone antagonists, angiotensin receptor blockers

**This article provides an update on the drug treatment for heart failure (HF) mostly based on the recent clinical guidelines issued by the National Institute of Clinical Excellence (NICE).[1] New high quality evidence from randomised controlled trials has resulted in greater value being given to the use of beta-blockers (BBs) and to the use of the hydralazine-nitrate combination. The importance of monitoring laboratory and clinical parameters to ensure safe and effective drug treatment is also highlighted.**

## Introduction

HF occurs when the heart is unable to deliver blood and oxygen at a rate that meets the requirements of the body. It is characterised by symptoms of breathlessness, fatigue upon exertion, and signs of fluid retention. Some people with HF have left ventricular systolic dysfunction (LVSD), with reduced left ventricular ejection fraction, typically identified on echocardiography. Others have HF with a preserved ejection fraction. Most of the evidence relating to drug treatment is for HF due to LVSD.[1] Two classifications of the severity of HF are commonly employed (Figure 1). The New York Heart Association (NYHA) functional classification is based on symptoms and exercise capacity and is employed routinely in most randomized clinical trials.[2] The American College of Cardiology/American Heart Association (ACC/AHA) classification describes HF in stages based on structural changes and symptoms.[3]

The most common cause of HF is coronary artery disease, which accounts for around 70% of cases.[4] Other causes are hypertension, valvular disease, and arrhythmias such as atrial fibrillation. Advancing age, smoking, hyperlipidaemia and diabetes mellitus are among the associated risk factors. Infections, anaemia, alcohol abuse, side effects of medication such as non-steroidal anti-inflammatory drugs, and non-compliance with prescribed treatment can also exacerbate HF.[5]

In Europe, the prevalence of HF is between 2 and 3% and rises sharply at around 75 years of age; the prevalence in seventy to eighty year-old people is between 10 and 20%. In younger age groups HF is more common in men because the most common cause, coronary heart disease, occurs in earlier decades. In the elderly, the prevalence is equal between the sexes.[5] The overall prevalence of HF is increasing because of ageing of the population, improved survival of patients with coronary artery disease and more effective treatments for HF.[6]

## Drug treatment strategy

Patients with HF have a shorter life expectancy and experience symptoms that can reduce their quality of life. The aims of treatment are to reduce the risk of mortality, delay disease progression, control symptoms and improve quality of life.

Over the past two decades, the therapeutic approach to HF patients has undergone considerable change. Several drug classes have been introduced targeting the two biological pathways implicated in progression of the disease, the renin-angiotensin-aldosterone system and the sympathetic nervous system. Current treatment not only concerns symptomatic improvement, but increasingly focuses on delaying disease progression and on reducing mortality.

### Angiotensin-converting enzyme inhibitors

There is evidence to support the use of angiotensin-converting enzyme inhibitors (ACEIs) in all patients with LVSD. ACEIs improve symptoms, reduce hospitalisation rate, and improve survival rate.[7,8,9,10,11] ACEIs should be offered to all patients with HF due to LVSD (Figure 2).[1]

ACEIs should be started at a low dose and titrated upwards at short intervals of at least two weeks until the optimal tolerated or target dose is achieved. The safety of treatment with ACEIs is best achieved by monitoring serum potassium, urea, creatinine and estimated glomerular filtration rate (eGFR) before the initiation of ACEIs, one to two weeks following each dose increment, and then every three to six-months thereafter.[1,5] Hyperkalaemia is

**Figure 1: Classification of heart failure by structural abnormality (ACC/AHA), or by symptoms relating to functional capacity (NYHA)**

| ACC/AHA stages of heart failure | | NYHA functional classification | |
|---|---|---|---|
| **Stage of heart failure based on structure and damage to heart muscle** | | **Severity based on symptoms and physical activity** | |
| **Stage A** | At high risk for developing heart failure. No identified structural or functional abnormality; no signs or symptoms. | **Class I** | No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea. |
| **Stage B** | Developed structural heart disease that is strongly associated with the development of heart failure, but without signs or symptoms. | **Class II** | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea. |
| **Stage C** | Symptomatic heart failure associated with underlying structural heart disease. | **Class III** | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnoea. |
| **Stage D** | Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy. | **Class IV** | Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased. |

ACC American College of Cardiology; AHA American Heart Association; NYHA New York Heart Association

a potential problem during therapy. Mildly raised potassium levels (5.0-6.0mmol/L) can often be managed by dietary modifications (foods containing high levels of potassium e.g. banana, tomatoes and citrus fruits to be avoided). Cessation of treatment should only be considered if serum potassium is more than 6mmol/L.[1,5] An increase in creatinine is expected when an ACEI is initiated, but the action taken should be determined by the extent of the rise. According to guidelines from the European Society of Cardiology, an increase in creatinine of up to 50% from baseline or to an absolute concentration of 265µmol/L, whichever is lower, is acceptable. If the creatinine rises above 265µmol/L, but below 310µmol/L, the dose of ACEI should be halved. If the creatinine rises to 310µmol/L or above, the ACEI should be stopped immediately.[5] According to NICE guidelines, a change in creatinine of less than 30% or in eGFR of less than 25% is acceptable; if the change is greater, the ACEI should be stopped or the dose reduced to a previously tolerated lower dose.[1]

Cough is a common adverse effect of ACEIs and switching to an angiotensin receptor blocker is recommended.[5] Symptomatic hypotension (e.g. dizziness) is also common but often improves with time, and patients should be reassured. Reducing the dose of diuretics and other hypotensive agents should be considered. Asymptomatic hypotension does not require intervention.[5]

*Angiotensin receptor blockers*
There is significant evidence supporting to use of angiotensin receptor blockers (ARBs) in the management of HF, although this is weaker than that for ACEIs.[12,13,14,15,16,17] Unlike ACEIs they do not cause dry cough, one of the most common causes of stopping ACEI therapy. When patients are intolerant of ACEIs, the introduction of ARBs is proposed as an alternative.[1] ARBs are also recommended as second-line treatment if a patient remains symptomatic despite optimal therapy with an ACEI and a BB, especially if the patient has mild to moderate HF (NYHA class II-III) (figure 2).[1] Monitoring of serum potassium, urea, creatinine and eGFR for signs of hyperkalaemia or renal impairment is recommended as for ACEIs.

*Beta blockers*
Patients who have HF with LVSD should be considered for the introduction of BBs. In these patients BBs have been shown to reduce morbidity, hospitalisation and mortality. BBs of proven efficacy in HF include carvedilol, nebivolol, bisoprolol and metoprolol succinate.[18,19,20,21,22,23,24] According to the recent NICE guidelines (figure 2), both ACEIs and BBs licensed for HF should be offered to all patients with HF due to LVSD, using clinical judgement when deciding which drug to start first.[1] This recommendation resulted from evidence from the CIBIS III trial indicating that HF patients derived similar outcome of therapy with ACEIs followed by BBs, to those treated with BBs followed by ACEIs.[25] The clinical decision to use one of these two agents before the other depends on the clinical status of the patient. Several factors could affect the choice, including blood pressure, heart rate as well as the presence of symptomatic ischaemia, arrhythmias and other co-morbidities.[1]

BBs should not be withheld from older adults and patients with peripheral vascular disease (unless severe), erectile dysfunction, diabetes mellitus, interstitial pulmonary 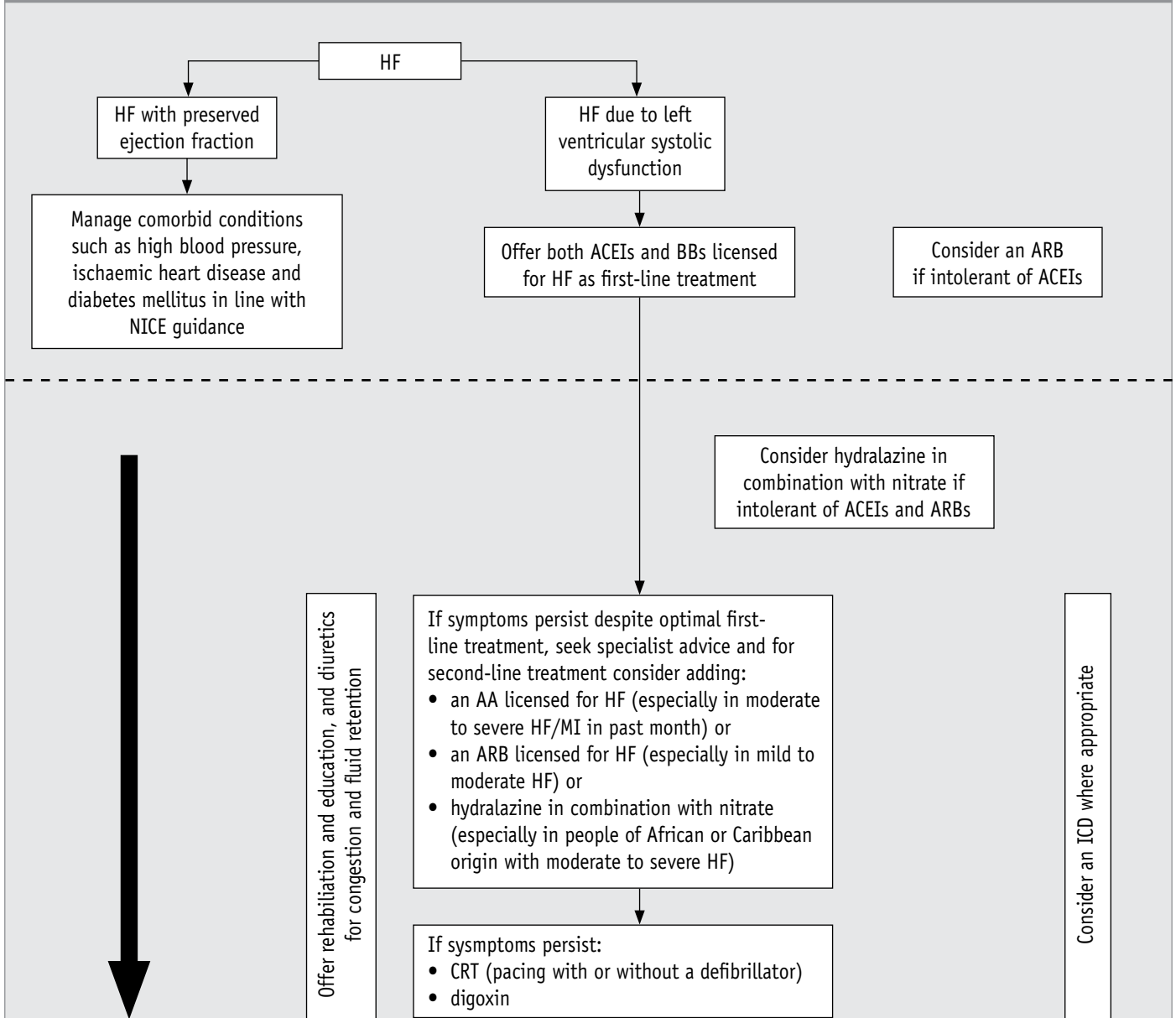disease and chronic obstructive pulmonary disease without reversibility. Stable patients who are already taking a BB for a concurrent disease (e.g. angina or hypertension) and who develop HF due to LVSD, should be switched to a BB licensed for HF.[1]

Treatment should be started in stable patients at low doses and up-titrated slowly at intervals of at least two to four weeks. It is important, during the up-titration of BBs, to monitor the patient's pulse rate, blood pressure and the clinical status, to avoid side effects such as symptomatic bradycardia and symptomatic hypotension. The up-titration should be undertaken gradually and slowly to achieve the target doses used in the clinical trials, if tolerated. The patient needs to be informed that transient pulmonary congestion could occur at times during up-titration of BBs.[1,5]

*Aldosterone antagonists*
There is evidence of enhanced activity of the renin-angiotensin-aldosterone system in patients with HF. The modulation of this system started with the introduction of ACEIs, and followed by the introduction of the ARBs in the treatment of HF. Spironolactone, an aldosterone antagonist (AA), was contra-indicated in combination with ACEIs, until the publication of the RALES study in 1999.[26] Evidence from this study indicated that moderately to severely symptomatic patients with HF (NYHA class III-IV), despite optimal medical therapy, attained lower hospitalisation rates and higher survival rates with the addition of spironolactone. A more recent trial investigating the newer AA, eplerenone, in patients with LVSD and clinical evidence of HF or diabetes mellitus within 14 days of a myocardial infarction (MI) also showed prognostic benefit in these patients.[27] In fact

**Figure 2: NICE algorithm for the treatment of heart failure (HF)[1]**

HF

↓

HF with preserved ejection fraction

HF due to left ventricular systolic dysfunction

↓

Manage comorbid conditions such as high blood pressure, ischaemic heart disease and diabetes mellitus in line with NICE guidance

Offer both ACEIs and BBs licensed for HF as first-line treatment

Consider an ARB if intolerant of ACEIs

Consider hydralazine in combination with nitrate if intolerant of ACEIs and ARBs

Offer rehabilitation and education, and diuretics for congestion and fluid retention

If symptoms persist despite optimal first-line treatment, seek specialist advice and for second-line treatment consider adding:
- an AA licensed for HF (especially in moderate to severe HF/MI in past month) or
- an ARB licensed for HF (especially in mild to moderate HF) or
- hydralazine in combination with nitrate (especially in people of African or Caribbean origin with moderate to severe HF)

If sysmptoms persist:
- CRT (pacing with or without a defibrillator)
- digoxin

Consider an ICD where appropriate

ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, BB beta-blocker, AA aldosterone antagonist, MI myocardial infarction, ICD implantable cardiovascular defibrillator, CRT cardiac resynchronisation therapy

**Initial and target doses of selected agents used in the treatment of HF[5,29]**

ACEI    enalapril 2.5mg once daily to 10-20mg twice daily
        lisinopril 2.5mg once daily to 35mg once daily
        perindopril arginine 2.5mg once daily to 5mg once daily

hydralazine 25mg three to four times daily to 50-75mg four times daily

ARB    candesartan 4mg once daily to 32mg once daily
       losartan 12.5mg once daily to 50mg once daily
       valsartan 40mg twice daily to 160mg twice daily

isosorbide dinitrate 20mg three times daily to 40mg three times daily

BB     carvedilol 3.125mg twice daily to 25-50mg twice daily
       nebivolol 1.25mg once daily to 10mg once daily

digoxin 62.5-125mcg once daily, up to 250mcg daily in atrial fibrillation

AA     spironolactone 12.5-25mg once daily to 50mg once daily

lower doses may be required in elderly and in renal or liver impairment

NICE guidelines (Figure 2) recommend that an AA should be considered as second-line treatment if a patient remains symptomatic despite optimal therapy with an ACEI and a BB especially if the patient has moderate to severe HF (NYHA class III–IV) or has had an MI within the past month. For patients who have had an acute MI and who have symptoms and/or signs of HF and LVSD, treatment with an AA licensed for post-MI treatment should be initiated within 3 to 14 days of the MI, preferably after ACEI therapy.[1] From a health economic point of view, the substantially lower cost of spironolactone compared to eplerenone suggests that spironolactone should be used in moderate to severe chronic HF, and eplerenone should be used in the patients with HF following MI.[1]

Treatment should be initiated at a low dose and up-titration considered only after four to eight weeks. Hyperkalaemia and a decline in renal function are common among patients prescribed AAs. Monitoring of serum potassium, urea, creatinine and eGFR is recommended at one, two, three and six months and six-monthly thereafter. The dose of AA should be halved if the potassium level rises to 5.5-5.9mmol/L and stopped immediately if potassium is above 6mmol/L. Similarly the dose should be halved if the creatinine level rises to below 220 µmol/L and stopped if creatinine is above 220µmol/L.[1,5]

### Diuretics
The use of diuretics in the treatment of HF is well established and essential for symptomatic relief when fluid overload is present. However, there is no evidence that loop and thiazide diuretics improve the prognosis of patients with HF. Diuretics should be titrated (up and down) according to need following the initiation of subsequent HF therapies. Monitoring of serum sodium, potassium, creatinine and eGFR should be carried out particularly in the acute stage when doses are increased. Care must be taken not to leave patients on unnecessarily high doses of diuretics; the dose should be decreased to the minimum required for symptom control.[1,5]

### Hydralazine plus nitrate
Evidence for the combination of hydralazine and nitrate comes from the AHEFT study in which the addition of the combination to optimal therapy (ACEI, BB and AA) in

black patients with moderate to severe HF (mainly NYHA class III) reduced morbidity and mortality.[28] Black patients of African and Caribbean descent have been found to derive less benefit than non-blacks from ACEIs in both HF and hypertension trials, and it is this group to which this evidence is applicable.

NICE guidelines (Figure 2) recommend that hydralazine in combination with nitrate be considered for patients with HF due to LVSD who are intolerant of ACEIs and ARBs. As second-line treatment the combination is to be considered if a patient remains symptomatic despite optimal therapy with an ACEI and a BB, especially if the patient is of African or Caribbean origin and has moderate to severe HF (NYHA class III-IV).[1]

Hypotension is a potential adverse effect with this drug combination although it often improves with time. If symptomatic, reducing the doses of other hypotensive agents (except ACEI/ARB/BB/AA) should be considered. Lupus-like syndrome due to the hydralazine component should be considered in the case of symptoms of arthralgia/muscle aches, joint pain or swelling, pericarditis, rash or fever.[5]

### Digoxin
Digoxin is one of the oldest known treatments for HF. Although it has an established role as a rate controller in patients with concomitant atrial fibrillation, its indication in HF patients in sinus rhythm is limited. According to NICE guidelines, digoxin is recommended for worsening or severe HF due to LVSD despite first- and second-line treatment for HF (Figure 2).[1]

Digoxin is well known for its potential for toxicity. Unwanted effects depend upon the concentration of the cardiac glycoside in the plasma and on the sensitivity of the conducting system or of the myocardium.[29] Regular monitoring of plasma digoxin concentration during maintenance treatment is not necessary but is indicated for initiation of treatment, confirmation or exclusion of toxicity, impaired renal function, co-administration of drugs which affect digoxin levels or to confirm patient compliance with the drug.[5,30] If an assay is indicated, blood should be sampled for digoxin at least six hours after an oral dose is administered. Samples should be taken at least eight days after initiation or change in dose. Sampling times should be recorded if assay results are to be interpreted correctly. The serum digoxin concentration should be interpreted in the clinical context as toxicity may occur even when the concentration is within the 'therapeutic range'. Various clinical factors predispose patients to digoxin toxicity. Hypokalaemia, hypercalcaemia and hypomagnesaemia all lead to an increase in responsiveness of cardiac tissues to the effects of digoxin. Correction of these underlying factors is therefore an important part of management.[30]

### Conclusion
Managing HF is a challenge and evidence-based guidelines should be utilised so as to provide optimal treatment and improve patient outcomes. Regular review including monitoring of both laboratory and clinical parameters is essential for safe and effective management.

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