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Chronic heart failure: epidemiology, investigation and management

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Abstract

Heart failure (HF) is a clinical syndrome characterized by dyspnoea, fatigue and fluid retention accompanied by objective evidence of cardiac dysfunction. The syndrome affects around 2% of the adult population, men more commonly than women (<80 years old), with the incidence and prevalence rising steeply with age. HF causes substantial morbidity and reduced life expectancy, and coronary artery disease accounts for two-thirds of cases in developed countries. Investigation is important to ascertain the diagnosis, identify the aetiology (which may be reversible) and give some indication of prognosis. The diagnosis of HF confers a significantly increased risk of hospital admission and death. Treatment has been revolutionized by large randomized controlled clinical trials studying the effects of antagonists of the renin–angiotensin–aldosterone, neutral endopeptidase and sympathetic nervous systems, and the effects of device therapy. Cardiac transplantation remains an option for patients who are severely symptomatic (and at high risk) despite optimal use of such therapy.

Keywords

Cardiomyopathy; epidemiology; heart failure; investigation; prognosis; treatment

Key points

- Heart failure (HF) is a syndrome with myriad causes; any reversible cause should be treated
- All patients with HF with reduced ejection fraction (HFrEF) should be treated with an angiotensin-converting enzyme inhibitor and (when euvolaemic) a β -adrenoceptor blocker
- Patients with severe left ventricular systolic dysfunction should also be given a mineralocorticoid receptor antagonist
- Sacubitril-Valsartan is indicated for patients with HFrEF who remain symptomatic despite optimal treatment
- Device therapy is suitable for selected patients with HF: cardiac resynchronisation therapy, implantable cardioverter-defibrillators and left ventricular assist devices
- Cardiac transplantation remains an option for those patients who worsen or fail to improve despite maximum disease-modifying therapy

Introduction

Heart failure (HF) is a clinical syndrome characterized by dyspnoea, fatigue and fluid retention accompanied by objective evidence of cardiac dysfunction. HF with reduced ejection fraction (HFrEF) is usually relatively

easy to diagnose using a range of non-invasive methods. However, the diagnosis of HF with preserved ejection fraction (HFpEF) is more difficult, and while it is often attributed to diastolic dysfunction, abnormalities of systolic and diastolic function frequently coexist.

Epidemiology

Prevalence

Population-based studies suggest a prevalence of HF of 2–3%, increasing to 7% in elderly individuals. The prevalence of HFpEF has been estimated at 9.7/1000 (44% of total HF prevalence). The prevalence of chronic HF is projected to increase by 50% in the next 20 years because of:

- an ageing population
- improved survival from other cardiovascular diseases
- improved survival rates for HF itself.

Incidence

UK population data report an annual incidence of 0.12% in ages 55–64 years, rising to 1.2% in those aged >85 – equivalent to 63,000 new cases of HF each year. Median age at diagnosis is 76 years, with a higher incidence in men than women at all ages (M:F around 1.8:1).

Prognosis

Recent European data suggest that all-cause mortality rates at 1 year are 17% and 7% for HF patients who are hospitalized and ambulatory, respectively. Equivalent rates for hospital admission are 44% and 32% in these groups.¹

Investigation

Investigation is important to ascertain the diagnosis, aetiology and prognosis. The most common investigations are as follows.

Electrocardiography – mandatory; it is abnormal in >90% of individuals with HF. Common abnormalities include:

- heart rate** – bradycardia (<60/minute) is common in patients taking a β -adrenoceptor antagonist and requires further investigation and management if associated with Mobitz type II or complete heart block. Tachycardia (>100/minute) is a possible cause, although more likely a consequence, of HF
- atrial fibrillation (AF)** – this has a prevalence of 10–50% in HF
- intraventricular conduction delay** – QRS duration >120 ms confers an increased risk of death. QRS>130 ms may identify patients for cardiac resynchronization therapy (CRT)
- regional versus local changes** – this suggests underlying coronary artery disease
- left ventricular hypertrophy** (e.g. secondary to hypertension).

Chest radiography – also mandatory:

- a normal chest X-ray does *not* exclude HF.
- cardiomegaly (cardiothoracic ratio >0.50), plus evidence of pulmonary congestion, suggests a cardiac abnormality.
- it can identify other causes of breathlessness.

Blood tests –

- urea and electrolytes** – HF is commonly associated with renal impairment and electrolyte disturbance; hyponatraemia indicates an adverse prognosis
- full blood count** – anaemia is common in HF and associated with adverse prognosis
- ferritin and iron studies** – haemochromatosis is an uncommon but reversible cause of HF. Iron deficiency is important to identify because intravenous iron supplementation may be appropriate (and of objective benefit)
- liver function tests** – these can be abnormal in the presence of hepatic congestion
- thyroid function tests** – thyrotoxicosis can cause left ventricular systolic dysfunction (LVSD) with or without AF, and hypothyroidism can accelerate coronary artery disease
- urate** – this is often elevated in patients taking diuretics; hyperuricaemia is associated with an adverse prognosis
- Brain natriuretic peptide (BNP; also N-terminal prohormone of BNP (NT-proBNP))** – this is useful in diagnosis (strong negative predictive value) (Figure 1) and determining prognosis.

Echocardiography – an accessible and non-invasive diagnostic test that can identify (and in some instances quantify) the following aspects of cardiac function:

- left ventricular dimensions and systolic function
- regional or localized wall abnormalities, suggestive of underlying coronary artery disease
- valve function
- right ventricular function
- estimation of pulmonary artery pressure
- presence or absence of a pericardial effusion
- markers of diastolic dysfunction.

Cardiac magnetic resonance – the gold standard for measurement of cardiac volumes and left ventricular mass. It helps to characterize cardiac tissue and identify areas of infarction or infiltration.

Other investigations may be useful:

- coronary angiography** – coronary artery disease is a potentially reversible cause of cardiac dysfunction. The STICHES trial has suggested that surgical revascularization in HF with minimal chest pain offers a prognostic advantage over medical therapy alone over the longer term (around 10 years)
- cardiopulmonary exercise testing** to quantify peak VO_2 (a useful prognostic marker)
- genetic testing**
- right heart catheterization** if candidacy for heart transplantation is being considered
- endomyocardial biopsy** if an infiltrative or rapidly progressive myocarditic process is a possibility.

Therapeutic options

The medical treatment of chronic HF has been revolutionized by large randomized controlled clinical trials studying the effects of antagonists of the renin–angiotensin–aldosterone, neutral endopeptidase and sympathetic nervous systems (Figure 2). Once established, HF is usually associated with poor prognosis and disabling symptoms, so therapy aims to reduce mortality and improve morbidity.

Primary prevention

It is of paramount importance to realize that prevention is better than cure. Treatment is recommended for patients with hypertension and with, or at high risk of, coronary artery disease, to delay or prevent the onset of HF. Treatment of other risk factors such as obesity and diabetes mellitus should be considered. In type 2 diabetes mellitus, SGLT2 inhibitors such as empagliflozin can delay the onset of HF and thus warrant specific consideration. In the setting of asymptomatic LVSD, angiotensin-converting enzyme (ACE) inhibitors are indicated, with the addition of a β -adrenoceptor blocker where the aetiology is ischaemic.

Disease-modifying therapy

ACE inhibitors

These are first-line agents that should be given to all patients with LVSD, whether symptomatic or not, combined with a diuretic if there is evidence of cardiac decompensation. In large clinical trials, ACE inhibitors achieve an average 20–25% relative risk reduction in morbidity and mortality. Their use is mandatory unless there is a firm contraindication – such as significant renal disease, angioedema or ACE inhibitor-induced cough – or the patient is taking sacubitril-valsartan (see below). Drugs with proven efficacy in clinical trials are enalapril, captopril, ramipril, lisinopril and trandolapril.

β -adrenoceptor antagonists

There is unequivocal evidence that the β -blockers bisoprolol, carvedilol and sustained-release metoprolol provide both a significant mortality and long-term symptomatic benefit in patients with all grades of HF, and in LVSD after myocardial infarction (MI). It is imperative that β -blockers are started only when patients are euvoelaemic, and then up-titrated slowly – ‘start low, go slow’. Chronic obstructive airways disease without airways reversibility and mild to moderate peripheral vascular disease are **not** contraindications to β -blocker therapy.

Mineralocorticoid receptor antagonists (MRAs)

Spironolactone reduces mortality and morbidity in patients with moderate to severe HF (New York Heart Association (NYHA) class III/IV) when used in addition to standard therapy (ACE inhibitors and β -blockers). More recently, eplerenone has been shown to have similar effects in patients with HF, or LVSD and diabetes

mellitus, after MI, and with severe LVSD and minimal symptoms. These drugs can impair renal function and cause significant hyperkalaemia.

Angiotensin receptor neprilysin inhibitors (ARNIs)

ARNIs are a new therapeutic class of medication acting conjointly on the renin–angiotensin and neutral endopeptidase systems. The sole drug in class available at this time is sacubitril-valsartan (LCZ696). This was compared with an ACE inhibitor (enalapril) in the PARADIGM-HF trial, which enrolled an ambulatory population with symptomatic HFrEF (left ventricular ejection fraction (LVEF) $\leq 40\%$).² Sacubitril-valsartan was superior to enalapril in reducing hospitalization for worsening HF, cardiovascular mortality and all-cause mortality (16% reduction in all-cause mortality compared with enalapril). Sacubitril-valsartan is thus recommended for patients with HFrEF who remain symptomatic despite an ACE inhibitor (or angiotensin II receptor blocker (ARB)), β -blocker and MRA. It replaces, rather than supplements, the ACE inhibitor or ARB.

Some important safety issues should be recalled during initiation of sacubitril-valsartan. Symptomatic hypotension is more common than with enalapril (although in the PARADIGM-HF trial fewer patients discontinued sacubitril-valsartan than enalapril). To minimize the risk of angioedema caused by overlapping ACE and neprilysin inhibition, the ACE inhibitor should be stopped at least 36 hours before initiating sacubitril-valsartan. Other major adverse effects include renal dysfunction and hyperkalaemia (although both of these occurred less frequently than those assigned to enalapril), and dose titration is managed in a similar manner to ACE inhibitors: with judicious clinical assessment and appropriately scheduled electrolyte and renal function checks. Combined treatment with an ACE inhibitor (or ARB) is contraindicated.

Ivabradine

Ivabradine is a specific inhibitor of the I_f current in the sinoatrial node but has no action on other channels in the heart or vascular system when used in therapeutic doses. It does not modify myocardial contractility or intracardiac conduction. Ivabradine should be considered for patients with HF in NYHA functional classes II–IV, with a heart rate ≥ 70 /minute and LVEF $\leq 35\%$ despite treatment with evidence-based doses of disease-modifying therapy (i.e. it is a fourth-line indication, after ACE inhibitors, β -blockers and MRAs). In the SHIFT study, ivabradine produced an 18% relative risk reduction in cardiovascular death/HF hospitalization in those already taking optimal medical therapy. In view of its mode of action, ivabradine has pharmacological effects only in sinus rhythm and is thus not indicated for patients in AF.

Angiotensin II receptor blockers

ARB are an effective alternative in truly ACE-intolerant individuals, although ACE inhibitors remain the first-line treatment. Indeed, the latest European Society of Cardiology (ESC) HF guidelines suggest that the addition of an ARB to ACE inhibitor and β -blocker therapy is indicated only in individuals intolerant of an MRA.¹ However, patient intolerant of ACE inhibitor therapy (e.g. because of cough) should next be considered for an ARNI rather than an ARB.

Hydralazine and nitrates

The combination of hydralazine and nitrates can be considered in patients intolerant of both ACE inhibitors and ARBs, or as an addition to either of these agents in African-American individuals.

Symptomatic therapy

Diuretics

Diuretics retain an important place in the management of symptoms and signs of fluid retention in HF. With diuretic resistance, sequential nephron blockade with a loop diuretic (e.g. furosemide, bumetanide) and a thiazide, or thiazide-like, diuretic (e.g. bendroflumethiazide, metolazone) may relieve fluid retention more effectively than further dose increases of loop diuretic. Renal function and serum potassium should be closely monitored. Diuretics do not confer a mortality benefit, and higher doses are associated with poorer outcome. Therefore, aim for as low a dose as possible in combination with fluid restriction where necessary (see below).

Digoxin

Current recommendations suggest digoxin use in patients who remain symptomatic despite maximal medical therapy, and to provide rate control in patients with AF. In the large trials using digoxin, patients with AF were excluded and no mortality benefit was demonstrated. Indeed, post hoc analyses have suggested higher mortality associated with treatment in some patient groups. Digoxin is therefore best reserved for patients who remain very symptomatic, with a large heart, and who require frequent hospitalization; it should be avoided in those with ventricular arrhythmias.

Other pharmacological therapy

The merits of warfarin therapy in patients with HF who are in sinus rhythm was investigated in the WARCEF study. The primary outcome of time to first event of death, ischaemic stroke or intracerebral haemorrhage was not different between aspirin or warfarin. A reduction in risk of ischaemic stroke with warfarin was offset by an increased risk of major haemorrhage. Whether rivaroxaban might be superior to placebo in patients with HF and coronary artery disease is currently being investigated.

Although statin therapy is of benefit in the primary and secondary prevention of coronary artery disease, patients with HF have usually been excluded from statin studies. Two large randomized trials, CORONA and GISSI-HF, were designed specifically to investigate statin effects in the HF population. Both showed no significant difference in the primary composite outcome of death from cardiovascular causes, non-fatal MI or non-fatal stroke between patients treated with rosuvastatin or placebo.

The aquaretic agent tolvaptan, a vasopressin V₂ receptor antagonist, was compared with placebo in >4000 patients hospitalized with HF in the EVEREST study; there were no differences in the primary end points of all-cause and cardiovascular death, or hospitalization for HF.

Drugs to avoid

It is important, if possible, to avoid drugs that might worsen HF, including non-steroidal anti-inflammatory drugs, rate-limiting calcium antagonists (diltiazem, verapamil), class I antiarrhythmic drugs (quinidine, procainamide, disopyramide), corticosteroids and tricyclic antidepressants.

Non-pharmacological intervention and lifestyle modification

Lifestyle modifications, such as cessation of smoking and alcohol consumption, weight loss and engagement in aerobic exercise, should be encouraged. Immunization against influenza and pneumococcus is recommended. Fluid intake should be restricted to 1.5–2 litres/day, and the patient advised of the importance of monitoring fluid balance (e.g. daily weights).. Salt-rich foods should be avoided, although salt restriction has not been shown to improve outcome.

Device therapy

Implantable cardioverter-defibrillators (ICDs)

Indications for ICD therapy in HF have emerged from the publication of several large randomized controlled trials:

- MADIT II study – a mortality benefit for ICDs in patients with ischaemic cardiomyopathy where LVEF was <30% at >40 days after MI
- SCD-HeFT study – LVEF ≤35% from either ischaemic or non-ischaemic aetiology in NYHA class II–III; the ICD group showed a reduction in all-cause mortality
- DANISH trial – patients with HFrEF of non-ischaemic aetiology (LVEF ≤35% and NYHA II–III or IV if awaiting CRT) randomized to optimal medical therapy with or without an ICD. Despite reducing sudden death, treatment with an ICD did not reduce overall mortality.

ESC HF guidelines suggest that ICDs should not be used in patients with NYHA class IV HF, except when they are candidates for cardiac transplantation or ventricular assist devices (VADs; although use of ICDs in VAD recipients is contentious).^{1,3}

Cardiac resynchronisation therapy

CRT aims to address the problem of ventricular dyssynchrony in HF by simultaneously stimulating the right ventricle and the left ventricular free wall. Leads are typically placed in the right atrium, right ventricular apex and coronary sinus. CRT reduces hospitalization and mortality, and improves quality of life and exercise capacity. To obtain maximal effects, biventricular pacing should be achieved as near to 100% of the time as is possible. The current ESC guidelines recommend the following:³

- CRT is recommended in symptomatic HF despite optimal medical therapy if:
 - LVEF \leq 35%
 - Sinus rhythm
 - QRS duration \geq 130 ms in left bundle branch block (LBBB) or \geq 150 ms in non-LBBB
- CRT should or may be considered in symptomatic HF despite optimal medical therapy if:
 - LVEF \leq 35%
 - Sinus rhythm
 - QRS duration \geq 130 ms in non-LBBB.

Despite a relative paucity of evidence for this therapy in patients with AF, CRT should be considered for patients with concomitant HFrEF (LVEF \leq 35% who are in NYHA class III–IV) and AF who have a QRS duration \geq 130 ms. CRT is contraindicated in patients with a QRS duration $<$ 130 ms – in this population, it *increases* mortality.

The above criteria derive from landmark clinical trials that established the morbidity and mortality benefits of CRT pacemaker and CRT defibrillator devices. However, approximately 30% of patients have been reported not to improve with CRT (non-responders).

Mechanical circulatory support

This is the umbrella term for a collection of technologies offering short- or long-term ventricular assistance for patients with HF. They are rapidly evolving and have an expanding indication. Long-term devices are generally reserved for patients with chronic HF, as a bridge to transplantation, transplant candidacy or myocardial recovery, or – in some countries – as destination therapy. In the UK, long-term VADs are currently indicated only as a bridge to transplantation. Short-term devices (e.g. extra-corporeal membrane oxygenation [ECMO], impella, and Centrimag) are used in an attempt to rescue patients at imminent risk of death, mostly in the setting of catastrophic cardiogenic shock.

Cardiac transplantation

Cardiac transplantation is the final intervention for patients who remain symptomatic despite optimal medical and device therapy. However, although the patient's condition should be sufficiently severe to justify this procedure, the individual should also be free of significant co-morbidities so that major cardiac surgery and the ensuing immunosuppressive regimen can be tolerated. Selecting patients for transplantation is difficult and traditionally involves clinical assessment and an assimilation of markers of HF severity.⁴ It is important to identify those patients at the highest risk of mortality before listing, as cardiac transplantation is far from a benign surgical procedure, with a 1-year mortality of approximately 17%, although delivering a median survival of $>$ 11 years.

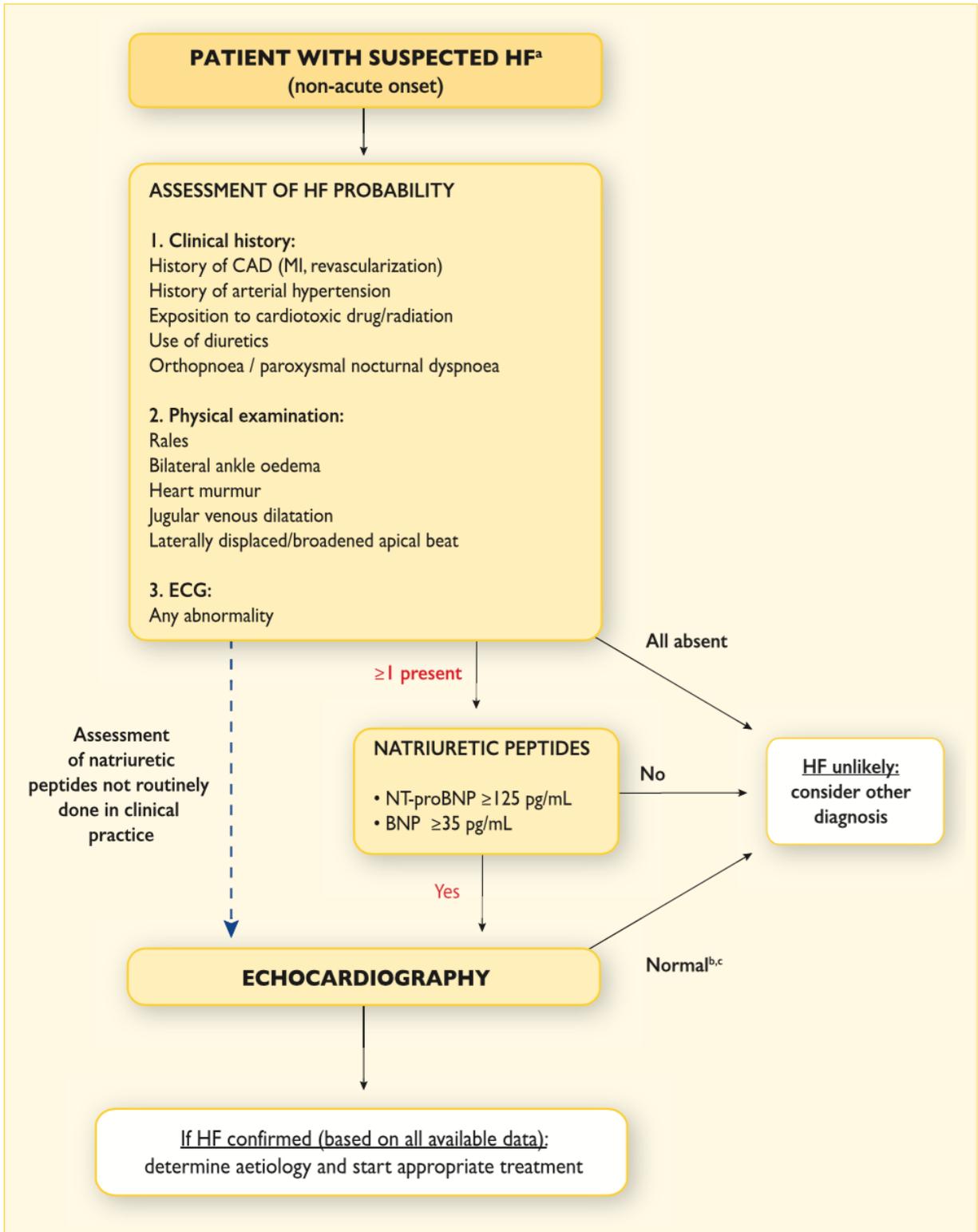


Figure 1 Diagnostic algorithm for the diagnosis of chronic heart failure
 CAD, coronary artery disease. For other abbreviations, see text.
 Source: Adapted from the European Society of Cardiology (from Ponikowski et al.¹).

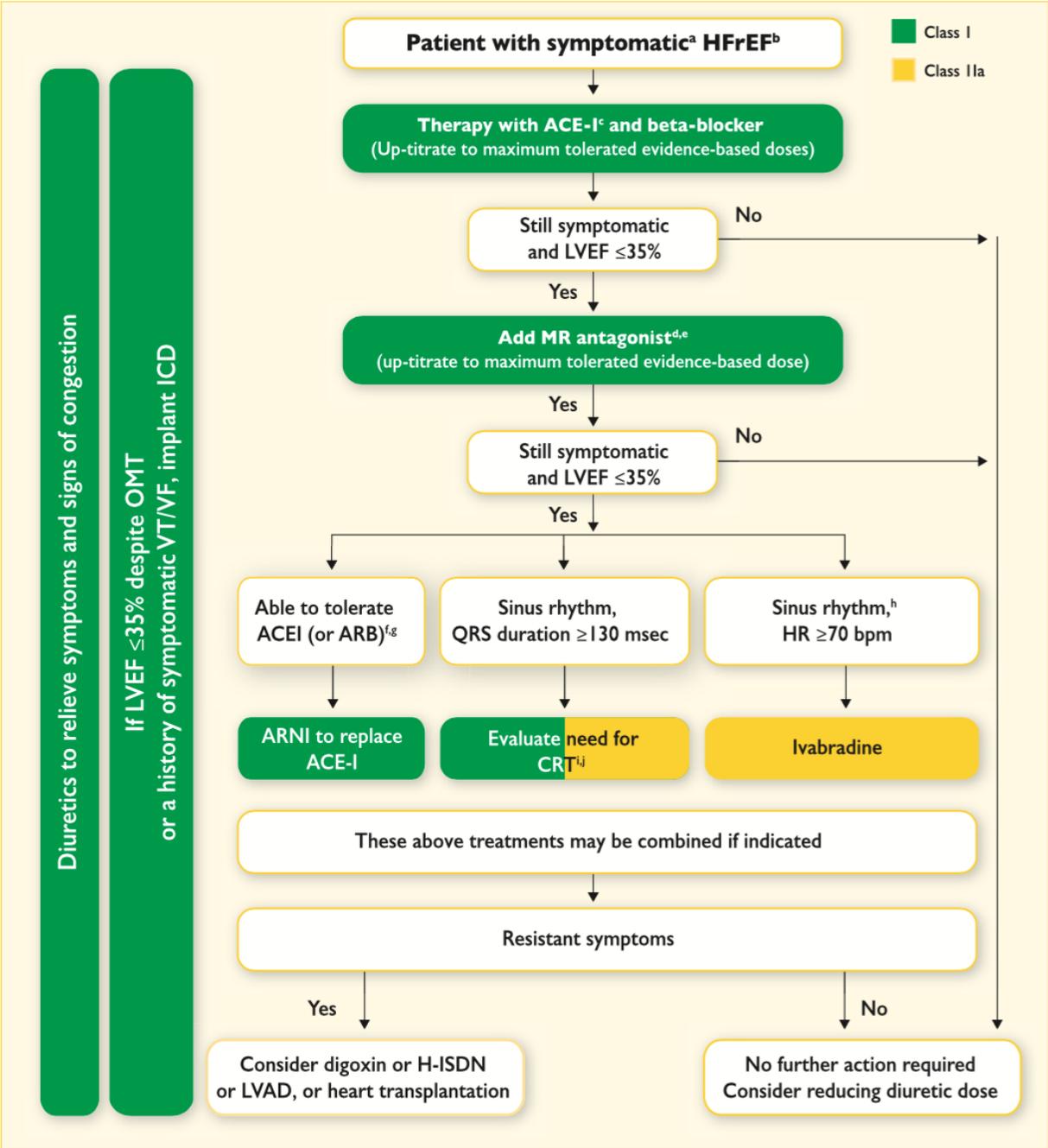


Figure 2 Algorithm for the treatment of HF-rEF

ACE-I, ACE inhibitor; H-ISDN, hydralazine–isosorbide dinitrate; LVAD, left ventricular assist device; VF, ventricular fibrillation; VT, ventricular tachycardia. For other abbreviations, see text.
 Source: Adapted from the European Society of Cardiology (from Ponikowski et al.¹).

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FURTHER READING

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

Question 1

A 65-year-old man presented with shortness of breath and tiredness. He had a past medical history of chronic obstructive pulmonary disease, hypertension and type 2 diabetes mellitus. He was taking ramipril, metformin and a salbutamol inhaler.

On clinical examination, his heart rate was 129 beats/minute and irregularly irregular. Blood pressure was 138/88 mmHg.

Investigations

- Chest X-ray showed a cardiothoracic ratio of 56% and clear lung fields
- ECG confirmed atrial fibrillation
- Echocardiogram showed left ventricular systolic dysfunction

Which of the following is the most appropriate rate-limiting medication in this patient?

- A. Digoxin
- B. Bisoprolol
- C. Amiodarone
- D. Diltiazem
- E. Ivabradine

Correct answer: B. Bisoprolol is the most appropriate treatment. COPD is not a contraindication in fixed airways obstruction. Digoxin (A) is an appropriate treatment but not the best as it confers no prognostic benefit in left ventricular systolic dysfunction (LVSD), and is less useful in rate control during exercise. Amiodarone (C) is an appropriate treatment but not the best (nor even second line) because of unwanted effects. Diltiazem (D) is contraindicated in LVSD because of its negative inotropic effects. Ivabradine (E) is ineffective in rate control in atrial fibrillation as it acts only on the sinoatrial node.

Question 2

A 42-year-old woman presented with a 6-month history of increasing breathlessness. She had been found to have chronic heart failure with severe left ventricular systolic dysfunction. She was already on optimal pharmacological therapy, and cardiac resynchronization therapy (CRT) was being considered as the next management step.

Which of the following combination of cardiac rhythm and conduction patterns is the evidence base most convincing for CRT?

- A. Right bundle branch block with a QRS duration of 165 ms and sinus rhythm
- B. Left bundle branch block with a QRS duration of 170 ms and atrial fibrillation
- C. Left bundle branch block with a QRS duration of 152 ms and sinus rhythm
- D. Non-specific intraventricular conduction delay with a QRS duration of 154 ms and sinus rhythm
- E. Right bundle branch block with a QRS duration of 143 ms and in atrial fibrillation

Correct answer: C. The bulk of evidence for CRT is for patients in sinus rhythm, severe LVSD and broad LBBB. There are little data to support the use of CRT in patients with atrial fibrillation (B and E), and non-LBBB morphologies (A, D and E). In right bundle branch block and sinus rhythm, cardiac resynchronization therapy should be considered if the QRS duration is >150 ms (A). CRT is now contra-indicated where the QRS is <130ms.

Question 3

A 78-year-old man presented with worsening exertional dyspnoea over several months. He was known to have severe left ventricular systolic dysfunction. He has multiple co-morbidities, including diabetes mellitus,

chronic renal impairment and peripheral vascular disease with previous femoro-popliteal bypass grafting. Cardiac medications were maximally tolerated doses of enalapril, carvedilol and eplerenone. Other medications included insulin, aspirin and atorvastatin.

Investigations

- Estimated glomerular filtration rate 47 ml/min/1.73 m² (>60)
- ECG showed sinus rhythm and a QRS duration of 110 ms
- Echocardiogram showed a left ventricular ejection fraction of 28%
- N-terminal pro-B-type natriuretic peptide concentration 3300 pg/ml (Normal: <125pg/ml)

What is the most appropriate next management step?

- A. Refer for assessment of suitability for cardiac transplantation
- B. Refer for cardiac resynchronisation therapy
- C. Add digoxin
- D. Add sacubitril-valsartan (and discontinue enalapril)
- E. Add candesartan (in addition to enalapril)

Correct answer: D. Sacubitril-valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) that acts conjointly on the renin–angiotensin and neutral endopeptidase systems, and has been found to be more effective than angiotensin-converting enzyme inhibition alone. Cardiac transplantation (A) is not appropriate, with contraindications including the patient's age, insulin-dependent diabetes mellitus and surgical-grade peripheral vascular disease. Cardiac resynchronization therapy (B) is contraindicated because of the narrow QRS duration. Digoxin (C) is appropriate, but not before sacubitril-valsartan (or ivabradine) has been tried. Candesartan (E) in addition to enalapril could be considered only if he was intolerant of a mineralocorticoid receptor antagonist (which he is not, because he is already taking one – eplerenone). However, even in that setting, this option would not be clearly better than sacubitril-valsartan.