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# 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure – Web Addenda

## The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

## Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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# 1. Web Tables

**Web Table 3.2 New York Heart Association functional classification based on severity of symptoms and physical activity**

| | |
|---|---|
| **Class I** | No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations. |
| **Class II** | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations. |
| **Class III** | Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations. |
| **Class IV** | Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased. |

**Web Table 3.3 ACCF/AHA stages of heart failure**

| | |
|---|---|
| **A** | At high risk for HF but without structural heart disease or symptoms of HF. |
| **B** | Structural heart disease but without signs or symptoms of HF. |
| **C** | Structural heart disease with prior or current symptoms of HF. |
| **D** | Refractory HF requiring specialized interventions. |

ACCF/AHA = American College of Cardiology Foundation/American Heart Association; HF = heart failure.

**Web Table 3.5 Markers of worse prognosis in patients with heart failure**

| | |
|---|---|
| Demographic data | Older age, male sex, low socio-economic status. |
| Severity of heart failure | Advanced NYHA Class, longer HF duration, reduced peak oxygen consumption, high VE-$VCO_2$ slope, Cheyne–Stoke ventilation, short 6-minute walking distance, reduced muscle strength, poor quality of life. |
| Clinical status | High resting heart rate, low blood pressure, clinical features of fluid overload (both pulmonary congestion and peripheral oedema, jugular venous dilatation, hepatomegaly), clinical features of peripheral hypoperfusion, body wasting, frailty. |
| Myocardial remodeling and severity of heart dysfunction | Low LVEF, LV dilatation, severe diastolic LV dysfunction, high LV filling pressure, mitral regurgitation, aortic stenosis, LV hypertrophy, left atrial dilatation, RV dysfunction, pulmonary hypertension, dyssynchrony, vast area of hypo/akinesis, wide QRS complex, presumed inflammation or infiltration on CMR, inducible ischaemia and poor viability on imaging. |
| Biomarkers of neurohormonal activation | Low sodium, high natriuretic peptides, high plasma renin activity, high aldosterone and catecholamines, high endothelin-1, high adrenomedullin, high vasopressin. |
| Other biomarkers | Markers of renal function, inflammationatory markers, cardiac stress markers, cardiac damage markers, metabolic markers, collagen markers, markers of organ damage/dysfunction. |
| Genetic testing (see section 5.10.1) | Certain mutations in inherited cardiomyopathies associated with high-risk of sudden cardiac death or rapid HF progression. |
| Cardiovascular co-morbidities | Atrial fibrillation, ventricular arrhythmia, non-revascularizable coronary artery disease, previous stroke/TIA, peripheral arterial disease. |
| Non-cardiovascular co-morbidities | Diabetes, anaemia, iron deficiency, COPD, renal failure, liver dysfunction, sleep apnoea, cognitive impairment, depression. |
| Non-adherence | Non-adherence with recommended HF treatment. |
| Clinical events | HF hospitalization, aborted cardiac arrest, ICD shocks. |

CMR=cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QRS = Q, R, and S waves (combination of three of the graphical deflections); RV = right ventricular; TIA = transient ischaemic attack; VE-$VCO_2$ = ventilatory equivalent ratio for carbon dioxide.

**Web Table 4.2 Typical demographics and co-morbidities associated with heart failure with preserved ejection fraction**

| |
|---|
| Advanced age |
| Arterial hypertension |
| Atrial fibrillation |
| Female gender |
| Kidney dysfunction |
| Metabolic syndrome |
| Obesity |
| Physical deconditioning |
| Pulmonary disease (e.g. COPD) |
| Pulmonary hypertension |
| Sleep apnoea |

COPD = chronic obstructive pulmonary disease.

**Web Table 4.3 Normal and abnormal values of echocardiographic indices of diastolic function of left ventricle at rest according to age categories, differentiated for gender. Values are presented as means (± standard deviations) (the cut-offs of these parameters have been derived from the following references).[65,70,72,80–86]**

| Parameter | Normal diastolic function | | | | | | Diastolic dysfunction | | |
|---|---|---|---|---|---|---|---|---|---|
| | 20–40 years | | 40–60 years | | ≥60 years | | Impaired relaxation | Pseudo-normal filling | Restrictive filling |
| | Male | Female | Male | Female | Male | Female | | | |
| MV-inflow | | | | | | | | | |
| MV-E (m/s) | 0.79 ± 0.14 | 0.84 ± 0.17 | 0.72 ± 0.16 | 0.77 ± 0.17 | 0.67 ± 0.15 | 0.72 ± 0.17 | | | |
| MV-A (m/s) | 0.50 ± 0.13 | 0.51 ± 0.12 | 0.61 ± 0.15 | 0.63 ± 0.14 | 0.73 ± 0.16 | 0.76 ± 0.16 | | | |
| DecT (m/s) | 179.8 ± 46.4 | 176.7 ± 40.1 | 186.6 ± 52.8 | 188.2 ± 39.8 | 217.5 ± 69.7 | 201.5 ± 55.7 | >220 | 140–220 | <140 |
| E/A ratio (m/s) | 1.69 ± 0.52 | 1.72 ± 0.52 | 1.22 ± 0.31 | 1.26 ± 0.43 | 0.96 ± 0.27 | 0.99 ± 0.31 | <1.0 | 1.0–2.0 | >2.0 |
| Ivrt (m/s) | | | | | | | >110 | 60-100 | <60 |
| Tissue Doppler | | | | | | | | | |
| e' septal (cm/s) | 11.9 ± 2.7 | 12.3 ± 2.3 | 9.8 ± 2.6 | 9.7 ± 2.5 | 7.3 ± 2.2 | 7.9 ± 2.3 | <8 | <8 | <8 |
| e' lateral (cm/s) | 16.2 ± 3.6 | 16.6 ± 3.2 | 12.6 ± 3.0 | 12.4 ± 3.0 | 9.5 ± 2.1 | 9.7 ± 3.2 | <10 | <10 | <10 |
| e' mean sept-lat (cm/s) | 14.0 ± 2.9 | 14.5 ± 2.4 | 11.2 ± 2.4 | 11.1 ± 2.5 | 8.5 ± 1.9 | 8.8 ± 2.6 | | | |
| E/e' septal | 6.9 ± 1.7 | 6.9 ± 1.6 | 7.8 ± 2.4 | 8.2 ± 2.2 | 9.8 ± 3.0 | 9.7 ± 2.6 | | | |
| E/e' lateral | 5.0 ± 1.3 | 5.2 ± 1.3 | 6.1 ± 2.2 | 6.5 ± 2.3 | 7.6 ± 2.1 | 7.9 ± 2.2 | | | |
| E/e' mean sep-lat | 5.8 ± 1.4 | 5.9 ± 1.3 | 6.7 ± 2.1 | 7.2 ± 2.0 | 8.4 ± 2.2 | 8.6 ± 2.2 | | ≥13 | ≥13 |

DecT = deceleration time of MV-E; e′ = early diastolic tissue velocity; E/e′ = a ratio between early mitral inflow velocity and mitral annular early diastolic velocity; IVRT = isovolumetric relaxation time; MV = mitral valve; MV-A = mitral valve late diastolic inflow; MV-E = mitral valve early diastolic inflow.

**Web Table 4.4 Diagnostic tests for specific causes of heart failure with preserved ejection fraction**

| |
|---|
| Genetic testing (e.g. for ATTR amyloidosis and HCM; see also section 5.10.1) |
| Bence-Jones proteinuria (AL amyloidosis) |
| 99mTc-DPD scintigraphy (wild-type transthyretrin amyloidosis) |
| Eosinophilia, IL-2 receptor, ACE (sarcoidosis) |
| Hs troponin, CK, CK-MB (myocarditis) |
| *Borellia burgdorferi* IgM (borreliosis) |
| HIV serology (HIV cardiomyopathy) |
| *Tryponosoma cruzi* serology (Chagas disease) |
| Serum ferritin, genetic testing (haemochromatosis) |
| Alpha-galactosidase activity in leucocytes (Fabry disease) |
| Eosinophilia (Löffler endomyocarditis) |

ACE = angiotensin-converting enzyme; AL = amyloid light-chain; ATTR = transthyretin mediated amyloidosis; CK = creatine kinase; CK-MB = creatine kinase MB; HCM = hypertrophic cardiomyopathy; HIV = human immunodeficiency virus; hs = high sensitivity; IL-2 = interleukin 2.

**Web Table 7.1 Major clinical trials of therapeutic interventions in patients with heart failure with reduced ejection fraction**

| Trial | Drug | Major inclusion criteria | Mean follow-up | Impact of treatment on primary endpoint | Other results |
|---|---|---|---|---|---|
| **ACEIs** | | | | | |
| CONSENSUS [2] | Enalapril (*n* = 127) vs placebo (*n* = 126). | Congested HF, NYHA IV, cardiomegaly on chest X-ray. | 0.5 y | All-cause mortality reduced by 40% at 6 months (26% vs 44%, *P* =0.002) and by 31% at 12 months (52% vs 36%, *P* =0.001). | - |
| SOLVD-TREATMENT [168] | Enalapril (*n* = 1285) vs placebo (*n* = 1284). | LVEF ≤35%; NYHA I–IV (90% NYHA II–III). | 3.5 y | All-cause mortality reduced by 16% (35% vs 40%) (*P* =0.004). | Reduction in combined all-cause mortality and HF hospitalization rate by 26% (*P* < 0.0001). |
| ATLAS [169] | High (*n* = 1568) vs low (*n* = 1596) dose of lisinopril. | LVEF ≤30%; NYHA II–IV. | 3.8 y | All-cause mortality was non-signficantly reduced by 8% (43% vs 45%, *P* =0.13). | Trend towards a reduction in cardiovascular mortality by 10% (*P* =0.07) Reduction in combined all-cause mortality or HF hospitalization rate by 15% (*P* < 0.001). |
| **Beta-blocker** | | | | | |
| COPERNICUS [170] | Carvedilol (*n* = 1156) vs placebo (*n* = 1133). | LVEF <25%, NYHA IV. | 0.9 y | All-cause mortality reduced by 35% (11% vs 17%) (*P* < 0.001). | Reduction in combined all-cause mortality and any hospitalization rate by 24% (*P* < 0.001). |
| CIBIS-II [171] | Bisoprolol (*n* = 1327) vs placebo (*n* = 1320). | LVEF ≤35%, NYHA III–IV. | 1.3 y | All-cause mortality reduced by 34% (12% vs 17%) (*P* < 0.001) | Reduction in combined cardiovascular mortality or cardiovascular hospitalization rate by 21% (*P* < 0.001). |
| MERIT-HF [172] | Metoprolol CR/XL (*n* = 1991) vs placebo (*n* = 2001). | LVEF ≤40%, NYHA II–IV. | 1.0 y | All-cause mortality reduced by 34% (7% vs 11%) (*P* < 0.001). | Reduction in the risk of cardiovascular death by 38% (*P* < 0.001), sudden death by 41% (*P* < 0.001) and death from aggravated HF by 49% (*P* =0.002). |
| SENIORS [173] | Nebivolol (*n* = 1067) vs placebo (*n* = 1061). | Age ≥70 y, HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months. | 1.8 y | Combined all-cause mortality and cardiovascular hospitalization rate reduced by 14% (31% vs 35%, *P* =0.04). | - |
| **MRAs** | | | | | |
| RALES [174] | Spironolactone (*n* = 822) vs placebo (*n* = 841). | LVEF≤35%, NYHA III–IV at enrolment and NYHA IV in 6 recent months. | 2.0 y | All-cause mortality reduced by 30 (35% vs 46%) (*P* < 0.001). | Reduction in a cardiac hospitalization rate by 35% (*P* < 0.001). |
| EMPHASIS-HF [175] | Eplerenone (*n* = 1364) vs placebo (*n* = 1373). | NYHA II, LVEF ≤30% or LVEF 30–35% with QRS >130 ms, cardiovascular hospitalization in recent 6 months or BNP ≥250 pg/mL or NT-proBNP ≥500 pg/mL in men and ≥750 pg/mL in women. | 1.8 y | Combined cardiovascular mortality or HF hospitalization rate reduced by 37% (18% vs 26%, *P* < 0.001). | Reduction in all-cause mortality by 24% (*P* =0.008) and cardiovascular mortality by 24% (*P* =0.01) Reduction in HF hospitalization rate by 42% (*P* < 0.001). |
| **ARNI** | | | | | |
| PARADIGM-HF[167] | Sacubitril/valsartan (*n* = 4187) vs enalapril (*n* = 4212). | NYHA II–IV, LVEF ≤40% (amended to LVEF ≤35%), BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL, or if HF hospitalization within recent 12 months BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL. | 2.3 y | Composite of death from cardiovascular causes or a first HF hospitalization reduced by 20% (22% vs 27%, *P* < 0.001). | Reduction in all-cause mortality by 16% (*P* < 0.001) and cardiovascular mortality by 20% (*P* < 0.001). Reduction in HF hospitalization rate by 21% (*P* < 0.001). |
| **If-channel blocker** | | | | | |
| SHIFT [176] | Ivabradine (*n* = 3268) vs placebo (*n* = 3290). | LVEF ≤35%, NYHA II–IV, HF hospitalization in recent 12 months, sinus rhythm, heart rate ≥70 bpm. | 1.9 y | Combined cardiovascular mortality or HF hospitalization rate reduced by 18% (24% vs 29%, *P* < 0.001). | Reduction in HF hospitalization rate by 26% (*P* < 0.001). Reduction in HF-related mortality by 26% (*P* =0.01). |
| **ARB** | | | | | |
| CHARM-Added[177] | Candesartan (*n* = 1276) vs placebo (*n* = 1272). | LVEF ≤40%, NYHA II–IV, treatment with ACE-I. | 3.4 y | Combined cardiovascular mortality or HF hospitalization rate reduced by 15% (38% vs 42%, *P* =0.01). | - |

*continued*

**Web Table 7.1 Major clinical trials of therapeutic interventions in patients with heart failure with reduced ejection fraction (continued)**

| Trial | Drug | Major inclusion criteria | Mean follow-up | Impact of treatment on primary endpoint | Other results |
|---|---|---|---|---|---|
| **ARB (continued)** | | | | | |
| CHARM-Alternative[178] | Candesartan (*n* = 1013) vs placebo (*n* = 1015). | LVEF ≤40%, NYHA II–IV, intolerant to ACE-I. | 2.8 y | Combined cardiovascular mortality or HF hospitalization rate reduced by 23% (33% vs 40%, *P* < 0.001). | - |
| Val-HeFT[179] | Valsartan (*n* = 2511) vs placebo (*n* = 2499). | LVEF <40%, NYHA II–IV, treatment with ACE-I, LVID >2.9 cm/BSA. | 1.9 y | All-cause mortality was similar in both groups (19.7% vs 19.4%, *P* =0.80)<br>Reduction in a co-primary combined endpoint of all-cause death, cardiac arrest with resuscitation, HF hospitalization, or i.v. administration of inotropic or vasodilator drugs for ≥4 hours without hospitalization by 13% (29% vs 32%, *P* =0.009). | - |

ACE = angiotensin-converting enzyme; ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; ATLAS = Assessment of Treatment with Lisinopril And Survival; BNP = B-type natriuretic peptide; bpm = beats per minute; BSA = body surface area; CHARM-Added = Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHARM-Alternative = Candesartan in heart failure assessment of reduction in mortality and morbidity; CIBIS II = Cardiac Insufficiency Bisoprolol Study II; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; i.v. = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; LVID = left ventricular internal dimension; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; QRS = Q, R, and S waves (combination of three of the graphical deflections); RALES = Randomized Aldactone Evaluation Study; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure; SHIFT = Systolic Heart failure treatment with the If inhibitor ivabradine Trial; SOLVD = Studies of Left Ventricular Dysfunction; Val-HeFT = Valsartan Heart Failure Trial; y = years.

**Web Table 7.4 Practical guidance on the use of angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers) in patients with heart failure with reduced ejection fraction[a]**

**WHY?**

To improve symptoms and exercise capacity, reduce the risk of HF hospitalization and increase survival.

**IN WHOM AND WHEN?**

**Indications:**
1. Potentially all patients with HF and an LVEF <40%.
2. First-line treatment (along with a beta-blockers and an MRA) in patients with HF NYHA Class II–IV, start as early as possible in the course of disease.
3. ACE-Is are also of benefit in patients with asymptomatic LV systolic dysfunction (NYHA Class I).

**Contra-indications:**
1. History of angioedema.[b]
2. Known bilateral renal artery stenosis.
3. Pregnancy/risk of pregnancy.
4. Known allergic reaction/other adverse reaction (drug-specific).

**Cautions/seek specialist advice:**
1. Significant hyperkalaemia (K+ >5.0 mmol/L).
2. Significant renal dysfunction (creatinine >221 μmol/L [>2.5 mg/dL] or eGFR <30 mL/min/1.73 $m^2$).
3. Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg).
4. Drug interactions to look out for:
   - o K+ supplements/ K+-sparing diuretics, e.g. amiloride and triamterene (beware combination preparations with furosemide).
   - o MRAs.
   - o Renin inhibitors[c].
   - o NSAIDs[d].
   - o Trimethoprim/trimethoprim-sulfamethoxazole.
   - o 'Low-salt' substitutes with a high K+ content.

**WHICH ACE-INHIBITOR AND WHAT DOSE? – see also Table 7.2**

Captopril: starting dose 6.25 mg *t.i.d.*, target dose 50 mg *t.i.d.*
Enalapril: starting dose 2.5 mg *b.i.d.*, target dose 20 mg *b.i.d.*
Lisinopril: starting dose 2.5–5.0 mg *o.d.*, target dose 20–35 mg *o.d.*
Ramipril: starting dose 2.5 mg *o.d.*, target dose 10 mg *o.d.*
Trandolapril: starting dose 0.5 mg *o.d.*, target dose 4 mg *o.d.*

**WHERE?**

- In the community in stable patients (NYHA Class IV/patients with severe HF and those with a current/recent exacerbation should be referred for specialist advice).
- In patients hospitalized with worsening HF – after stabilizing, relieving congestion, and, if possible, restoring 'euvolaemia' (but ideally before discharge).
- Other exceptions – see 'Cautions/seek specialist advice'.

**HOW TO USE?**

- Check renal function and electrolytes.
- Start with a low dose (see Table 7.2).
- Double the dose at not less than 2-week intervals in the community. More rapid dose up-titration may be carried out in patients in hospital or who are otherwise closely monitored, tolerability permitting.
- Aim for target dose (see above) or, failing that, the highest tolerated dose (remember: some ACE-I (or ARB) is better than no ACE-I).
- Re-check blood chemistry (urea/BUN, creatinine, K+) 1–2 weeks after initiation and 1–2 weeks after final dose titration.
- Monitor blood chemistry 4 monthly thereafter.
- When to stop up-titration, reduce dose, stop treatment–see PROBLEM SOLVING.
- It is very rarely necessary to stop an ACE-I (or ARB), and clinical deterioration is likely if treatment is withdrawn. Ideally, specialist advice should be sought before treatment discontinuation.
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring and dose up-titration.

**PROBLEM SOLVING**

**Asymptomatic low blood pressure:**
- Does not usually require any change in therapy.

**Symptomatic hypotension:**
- Dizziness/light headedness is common and often improves with time–patients should be reassured.
- Reconsider need for nitrates, calcium-channel blockers,[e] and other vasodilators and reduce dose/stop, if possible.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

**Cough:**
- Cough is common in patients with HF, many of whom have smoking-related lung disease.
- Cough is also a symptom of pulmonary oedema, which should be excluded when a new worsening cough develops.
- ACE-I-induced cough does not always require treatment discontinuation.
- When a troublesome cough does develop (e.g. one stopping the patient from sleeping) and can be proved to be due to ACE-inhibition (i.e. recurs after ACE-I withdrawal and re-challenge), substitution of an ARB is recommended.

*continued*

**Web Table 7.4 Practical guidance on the use of angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers) in patients with heart failure with reduced ejection fraction[a] (continued)**

| PROBLEM SOLVING |
|---|
| **Worsening renal function and hyperkalaemia:**<br>• Some rise in urea (BUN), creatinine, and potassium is to be expected after an ACE-I; if an increase is small and asymptomatic, no action is necessary.<br>• An increase in creatinine of up to 50% above baseline, or 266 μmol/L (3 mg/dL)/eGFR <25 mL/min/1.73 m$^2$, whichever is the smaller, is acceptable.<br>• An increase in potassium to ≤5.5 mmol/L is acceptable.<br>• If urea, creatinine, or potassium does rise excessively, consider stopping concomitant nephrotoxic drugs (e.g. NSAIDs[d]) and other potassium supplements or retaining agents (triamterene, amiloride) and, if no signs of congestion, reducing the dose of diuretic.<br>• If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE-I (or ARB) should be halved and blood chemistry re-checked within 1–2 weeks; if there is still an unsatisfactory response, specialist advice should be sought.<br>• If potassium rises to >5.5 mmol/L or creatinine increases by >100% or to >310 μmol/L (3.5 mg/dL)/eGFR <20 mL/min/1.73 m$^2$, the ACE-I (or ARB) should be stopped and specialist advice sought.<br>• Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued. |
| **ADVICE TO PATIENT** |
| • Explain expected benefits:<br>o Improved symptoms and exercise capacity.<br>o Prevention of worsening of HF leading to hospital admission.<br>o Increased survival.<br>• Symptoms improve within a few weeks to a few months after starting treatment.<br>• Advise patients to report principal adverse effects, (i.e. dizziness/symptomatic hypotension, cough)–see PROBLEM SOLVING.<br>• Advise patients to avoid NSAIDs[d] not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K+–see PROBLEM SOLVING. |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; *b.i.d.* = twice daily; BUN = blood urea nitrogen; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; LV = left ventricular; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; *o.d.* = once daily; *t.i.d.* = three times daily.

[a]The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.

[b]The safety of an ARB in patients developing angioedema with an ACE inhibitor is uncertain.

[c]Renin inhibitors are not recommended in HF.

[d]Avoid NSAIDs unless essential.

[e]Calcium-channel blockers should be discontinued unless absolutely necessary, and diltiazem and verapamil are potentially harmful in HFrEF because of their negative inotropic action.

**Web Table 7.5 Practical guidance on the use of beta-blockers in patients with heart failure with reduced ejection fraction[a]**

**WHY?**

To improve symptoms, reduce the risk of HF hospitalization and increase survival.

**IN WHOM AND WHEN?**

**Indications:**

1. Potentially all patients with stable mild or moderate systolic HF (LVEF <40%) (NYHA Class II-III).
2. First-line treatment, along with an ACE-I and an MRA, in patients with stabilized HF; start as early as possible in the course of disease.
3. Patients with severe HF also benefit from beta-blockers but treatment should be started under the care of a specialist.

**Contra-indications:**

1. Second- or third-degree AV block (in the absence of a permanent pacemaker).
2. Critical limb ischaemia.
3. Asthma (relative contra-indication): if cardio-selective beta-blockers are indicated, asthma is not necessarily an *absolute* contra-indication, but these medications should only be used under close medical supervision by a specialist, with consideration of the risks for and against their use[223,224]; COPD is not a contra-indication.
4. Known allergic reaction/other adverse reaction (drug-specific).

**Cautions/seek specialist advice:**

1. Severe (NYHA Class IV) HF.
2. Current or recent (<4 weeks) exacerbation of HF (e.g. hospital admission with worsening HF), heart block, or heart rate <50 bpm.
3. If persisting signs of congestion, hypotension (systolic <90 mmHg), raised jugular venous pressure, ascites, marked peripheral oedema - try to relieve congestion and achieve 'euvolaemia' before starting a beta-blocker.
4. Drug interactions to look out for (because of risk of bradycardia/atrioventricular block):
   - o Verapamil, diltiazem (should be discontinued).[b]
   - o Digoxin.
   - o Amiodarone.
   - o Ivabradine.

**WHICH BETA-BLOCKER AND WHAT DOSE? - See Table 7.2**

Bisoprolol: starting dose 1.25 mg *o.d.*, target dose 10 mg *o.d.*
Carvedilol: starting dose 3.125 mg *b.i.d.*, target dose 25 mg *b.i.d.*
Metoprolol succinate (CR/XL): starting dose 12.5–25 mg *o.d.*, target dose 200 mg *o.d.*
Nebivolol: starting dose 1.25 mg *o.d.*, target dose 10 mg *o.d.*

**WHERE?**

- In the community in stable patients (NYHA Class IV/patients with severe HF and those with a current/recent exacerbation should be referred for specialist advice).
- In patients hospitalized with worsening HF – after stabilizing, relieving congestion, and, if possible, restoring 'euvolaemia' (but ideally before discharge).
- Other exceptions–see 'Cautions/seek specialist advice'.

**HOW TO USE?**

- Start with a low dose in a stable condition (see Table 7.2).
- Double the dose at not less than 2-week intervals (slower up-titration may be needed in some patients).
- Aim for target dose (see above) or, failing that, the highest tolerated dose (remember: some beta-blocker is better than no beta-blocker).
- Monitor heart rate, blood pressure, and clinical status (symptoms, signs–especially signs of congestion, body weight).
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), and dose up-titration.
- When to stop up-titration, reduce dose, stop treatment–see PROBLEM SOLVING.

**PROBLEM SOLVING**

**Worsening symptoms or signs (e.g. increasing dyspnoea, fatigue, oedema, weight gain):**

- If increasing congestion, increase dose of diuretic or halve dose of beta-blocker (if increasing diuretic dose does not work).
- If marked fatigue (or bradycardia–see below), halve dose of beta-blocker (rarely necessary); review patient in 1–2 weeks; if not improved, seek specialist advice.
- If serious deterioration, halve dose of beta-blocker or stop this treatment (rarely necessary); seek specialist advice.

**Low heart rate:**

- If <50 bpm and worsening symptoms, halve dose of beta-blocker, or, if severe deterioration, stop beta-blocker (rarely necessary).
- Review need for other heart rate-slowing drugs (e.g. digoxin, amiodarone, diltiazem, or verapamil[b]).
- Arrange electrocardiogram to exclude heart block.
- Seek specialist advice.

**Asymptomatic low blood pressure:**

- Does not usually require any change in therapy.

**Symptomatic hypotension:**

- If dizziness, light headedness, or confusion and a low blood pressure, reconsider need for nitrates, calcium-channel blockers[b], and other vasodilators and reduce/stop, if possible.
- If no signs or symptoms of congestion, consider reducing diuretic dose.
- If these measures do not solve problem, seek specialist advice.

**ADVICE TO PATIENT**

- Explain expected benefits (see WHY?) and mention possibility of temporary adverse effects.
  - o Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival.
  - o Symptomatic improvement may develop slowly after starting treatment, sometimes taking 3–6 months or longer.
  - o Temporary symptomatic deterioration may occur during initiation or up-titration phase; in the long term beta-blockers improve well-being.

*continued*

**Web Table 7.5 Practical guidance on the use of beta-blockers in patients with heart failure with reduced ejection fraction[a] (continued)**

| **ADVICE TO PATIENT (continued)** |
|---|
| • Advise patient to report deterioration (see PROBLEM SOLVING) and that deterioration (tiredness, fatigue, breathlessness) can usually be easily managed by adjustment of other medication; patients should be advised not to stop beta-blocker therapy without consulting the physician.<br>• During initiation or up-titration phase to detect and to treat potential deterioration early, patients should be encouraged to weigh themselves daily (after waking, before dressing, after voiding, before eating) and to increase their diuretic dose should their weight increase, persistently (>2 days), by >1.5–2.0 kg/day. |

ACE = angiotensin-converting enzyme; AV = atrio-ventricular; *b.i.d.* = twice daily; bpm = beats per minute; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; *o.d.* = once daily.
Note: beta-blockers should not be stopped suddenly unless absolutely necessary (there is a risk of a 'rebound' increase in myocardial ischaemia or infarction and arrhythmias). Ideally, specialist advice should be sought before the treatment discontinuation.
[a] The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.
[b]Calcium-channel blockers should be discontinued unless absolutely necessary, and diltiazem and verapamil are potentially harmful in HFrEF because of their negative inotropic effect.

**Web Table 7.6 Practical guidance on the use of mineralocorticoid receptor antagonists in patients with heart failure with reduced ejection fraction[a]**

| |
|---|
| **WHY?** |
| To improve symptoms, reduce the risk of HF hospitalization and increase survival. |
| **IN WHOM AND WHEN?** |
| **Indications:**<br>1. Potentially all patients with persisting symptoms (NYHA Class II–IV) and an LVEF ≤35% despite treatment with an ACE-I (or ARB) and a beta-blocker. |
| **Contra-indications:**<br>1. Known allergic reaction/other adverse reaction (drug-specific). |
| **Cautions/seek specialist advice:**<br>1. Significant hyperkalaemia (K+ >5.0 mmol/L).[b]<br>2. Significant renal dysfunction (creatinine >221 μmol/L [>2.5 mg/dL] or eGFR <30 mL/min/1.73 m$^2$).[b]<br>3. Drug interactions to look out for:<br>o K+ supplements/ K+-sparing diuretics (e.g. amiloride and triamterene; beware combination preparations with furosemide).<br>o ACE-Is/ARBs/renin inhibitors.[c]<br>o NSAIDs.[d]<br>o Trimethoprim/trimethoprim-sulfamethoxazole.<br>o 'Low-salt' substitutes with a high K+ content.<br>o strong CYP3A4 inhibitors, e.g. ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, and nelfinavir (when eplerenone used). |
| **WHICH MRA AND WHAT DOSE? - see Table 7.2** |
| Eplerenone: starting dose 25 mg *o.d.*, target dose 50 mg *o.d.*<br>Spironolactone: starting dose 25 mg *o.d.*, target dose 50 mg *o.d.* |
| **WHERE?** |
| In the community or in the hospital.<br>Exceptions—see 'Cautions/seek specialist advice'. |
| **HOW TO USE?** |
| • Check renal function and electrolytes (particularly K+).<br>• Start with a low dose (see above).<br>• Consider dose up-titration after 4–8 weeks.<br>• Check blood chemistry at 1 and 4 weeks after starting/increasing dose and at 8 and 12 weeks; 6, 9, and 12 months; 4-monthly thereafter.<br>o If K+ rises above 5.5 mmol/L or creatinine rises to 221 μmol/L (2.5 mg/dL)/eGFR <30 mL/min/1.73 m$^2$, halve dose and monitor blood chemistry closely.<br>o If K+ rises to >6.0 mmol/L or creatinine to >310 μmol (3.5 mg/dL) eGFR <20 mL/min/1.73 m$^2$, stop MRA immediately and seek specialist advice.<br>• A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose up-titration. |
| **PROBLEM SOLVING** |
| **Worsening renal function/hyperkalaemia:**<br>• See HOW TO USE?<br>• The main concern is hyperkalaemia (>6.0 mmol/L); although this was uncommon in RALES and EMPHASIS-HF, it has been seen more commonly in clinical practice.<br>• Conversely, a high-normal K+ level may be desirable in patients with HF, especially if they are taking digoxin.<br>• It is important to avoid other K+-retaining drugs (e.g. K+-sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (e.g. NSAIDs[d]).<br>• The risk of hyperkalaemia and renal dysfunction when an MRA is given to patients already taking both an ACE-I and ARB is higher than when an MRA is added to just an ACE-I or ARB given singly; this triple combination of an ACE-Is, ARB and MRA is NOT recommended (see recommendations below).<br>• Some 'low-salt' substitutes have a high K+ content.<br>• Male patients treated with spironolactone may uncommonly develop breast discomfort or gynaecomastia (switching to eplerenone should be considered). |
| **ADVICE TO PATIENT** |
| • Explain expected benefits (see WHY?).<br>o Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission, and to increase survival.<br>o Symptomatic improvement occurs within a few weeks to a few months of starting treatment.<br>• Avoid NSAIDs[d] not prescribed by a physician (i.e. purchased over-the-counter) and salt substitutes high in K+.<br>• If diarrhoea/vomiting occurs or there is infection with fever leading to intense sweating patients should be aware the risk of dehydration and electrolyte imbalance, they should contact the physician/nurse. |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; MRA = mineralocorticoid receptor antagonist; NSAID = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; *o.d.* = once daily; RALES = Randomized Aldactone Evaluation Study.

[a]The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.

[b]It is extremely important to adhere to these cautions and doses to avoid serious hyperkalaemia.

[c]Renin inhibitors are not recommended in HF.

[d]Avoid NSAIDs unless essential.

**Web Table 7.7 Practical guidance on the use of diuretics in patients with heart failure**

**WHY?**

To relieve breathlessness and oedema in patients with symptoms and signs of congestion.

**IN WHOM AND WHEN?**

**Indications:**

1. Potentially all patients with symptoms and signs of congestion, irrespective of LVEF.
2. When used, should hould always be used in combination with an ACE-I (or ARB), a beta-blocker, and an MRA in patients with HFrEF (unless any of these drugs is not tolerated contra-indicated), until signs of congestion have been relieved.
3. Thaizde diuretics can be used in patients with preserved renal function and mild symptoms of congestion. However, the majority patients require loop diuretics (or combined with a thiazide diuretic and an MRA) due to the severity of HF symptoms and steadlily deterioriating kidney function.

**Contra-indications:**

1. Not indicated if the patient has never had symptoms or signs of congestion.
2. Known allergic reaction/other adverse reaction (drug-specific).

**Cautions/seek specialist advice:**

1. Significant hypokalaemia (K+ ≤3.5 mmol/L) – may be made worse by diuretic.
2. Significant renal dysfunction (creatinine >221 μmol/L [>2.5 mg/dL] or eGFR <30 mL/min/1.73 $m^2$) – may be made worse by diuretic or patient may not respond to diuretic (especially thiazide diuretic).
3. Symptomatic or severe asymptomatic hypotension (systolic blood pressure <90 mmHg) – may be made worse by diuretic-induced hypovolaemia.
4. Drug interactions to look out for:
   - o Combination with ACE-I ARB or renin inhibitors[a] –risk of hypotension (usually not a problem).
   - o Combination with other diuretics (e.g. loop plus thiazide)–risk of hypovolaemia, hypotension, hypokalaemia, and renal impairment.[b]
   - o NSAIDs[c] – may attenuate effects of diuretic.

**WHICH DIURETIC AND WHAT DAILY DOSE? - see Table 7.3**

**Loop diuretics:**
Furosemide: starting dose 20–40 mg, usual dose 40–240 mg
Bumetanide: starting dose 0.5–1.0 mg, usual dose 1–5 mg
Torasemide: starting dose 5–10 mg, usual dose 10–20 mg
**Thiazides:**
Bendroflumethiazide: starting dose 2.5, mg usual dose 2.5–10 mg
Hydrochlorothiazide: starting dose 25 mg, usual dose 12.5–100 mg
Metolazone: starting dose 2.5 mg, usual dose 2.5–10 mg
**Non-thiazide sulfonamide:**
Indapamide: starting dose 2.5 mg, usual dose 2.5–5 mg

**WHERE?**

In the community for most patients.

**HOW TO USE?**

- Check renal function and electrolytes.
- Start with a low dose (see Table 7.3), but an effective dose for a patient to achieving positive diuresis with a simultaneous reduction of body weight by 0.75–1,0 kg per day.
- Adjust dose according to symptoms and signs of congestion, blood pressure, and renal function. Use minimum dose necessary to maintain euvolaemia – the patient's 'dry weight' (i.e. to keep the patient free of symptoms and signs of congestion).
- Dose may need to be increased or decreased according to the patient's volume status (Remember that excessive diuresis is more dangerous than oedema itself).
- Re-check blood chemistry 1–2 weeks after initiation and after any increase in dose (urea/BUN, creatinine, K+).
- When to stop up-titration, reduce dose, stop treatment – see PROBLEM SOLVING.
- Patients can be educated to alter their own diuretic dose, according to need (based on symptoms, signs and weight changes – see Section 14).
- A specialist HF nurse may assist with education of the patient, follow-up (in person or by telephone), biochemical monitoring, and dose adjustment (including patient educated in dose adjustment).

**PROBLEM SOLVING**

**Asymptomatic low blood pressure:**
- Dose may be reduced if no symptoms or signs of congestion.

**Symptomatic hypotension:**
- Causing dizziness/light headedness – reduce dose if no symptoms or signs of congestion.
- Reconsider need for nitrates, CCBs[d] and other vasodilators.
- If these measures do not solve problem, seek specialist advice.

**Hypokalaemia/hypomagnaesaemia:**
- Increase ACE-I/ARB dose.
- Add MRA, potassium supplements; magnesium supplements.

**Hyponatraemia:**
- Volume depleted:
  - o Stop thiazide or switch to loop diuretic, if possible.
  - o Reduce dose/stop loop diuretics if possible.
- Volume overloaded:
  - o Fluid restriction.
  - o Increase dose of loop diuretic.
  - o Consider AVP antagonist (e.g. tolvaptan if available).
  - o i.v. inotropic support.
  - o Consider ultrafiltration.

*continued*

**Web Table 7.7 Practical guidance on the use of diuretics in patients with heart failure (continued)**

| PROBLEM SOLVING (continued) |
|---|
| **Hyperuricaemia/gout:**<br>• Consider allopurinol prophylaxis.<br>• For symptomatic gout use colchicine for pain relief.<br>• Avoid NSAIDs.<br>**Hypovolaemia/dehydration:**<br>• Assess volume status; consider diuretic dosage reduction.<br>**Insufficient diuretic response/diuretic resistance:**<br>• Check adherence and fluid intake.<br>• Increase dose of diuretic.<br>• Consider switching from furosemide to bumetanide or torasemide.<br>• Add MRA/increase dose of MRA.<br>• Combine loop diuretic and thiazide/metolazone.[b]<br>• Administer loop diuretic twice (or more times) daily or on empty stomach.<br>• Consider short-term i.v. Infusion of loop diuretic.<br>• Consider ultrafiltration.<br>**Renal impairment (rising creatinine/BUN–urea):**<br>• Check for hypovolaemia/dehydration.<br>• Exclude use of other nephrotoxic agents, e.g. NSAIDs, trimethoprim.<br>• Withhold MRA.<br>• If using concomitant loop and thiazide diuretic stop thiazide diuretic.<br>• Consider reducing dose of ACE-I/ARB.<br>• Consider haemofiltration/dialysis. |
| **ADVICE TO PATIENT** |
| • Explain expected benefits.<br>o Relieve breathlessness and oedema.<br>o Symptoms improve quickly – usually within days of starting treatment.<br>• Advise patients to report principal adverse effects (e.g. thirst) (avoid excessive consumption of hypotonic fluids, which can cause hyponatraemia) and dizziness/symptomatic hypotension – see PROBLEM SOLVING.<br>• Advise patients to avoid NSAIDs[c] not prescribed by a physician (i.e. purchased over-the-counter) – may cause diuretic resistance and renal impairment.<br>• Patient may be educated to adjust dose based on symptoms, signs, and changes in weight (if regular weighing).<br>• Dose may need to be decreased if fluid loss (e.g. due to diarrhoea/vomiting, excessive sweating). |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; AVP = arginine vasopressin; BUN = blood urea nitrogen; CCBs = calcium-channel blockers; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; i.v. = intravenous; MRA = mineralocorticoid receptor antagonist; NSAIDs = non-steroidal anti-inflammatory drugs.

[a]Renin inhibitors are not recommended in HF.

[b]Usually only needed for a short period – careful monitoring of blood chemistry is essential.

[c]Avoid NSAIDs unless essential.

[d]Calcium-channel blockers should be discontinued in patients with HFrEF unless absolutely necessary, and diltiazem and verapamil are potentially harmful in patients with HFrEF because of their negative inotropic action.

**Web Table 7.8 Practical guidance on the use of ivabradine in patients with heart failure with reduced ejection fraction[a]**

| **WHY?** |
|---|
| To reduce the risk of HF hospitalization and cardiovascular death. |
| **IN WHOM AND WHEN?** |
| **Indications:**<br>1 Patients with stable symptomatic HF (NYHA Class II–IV) and an LVEF ≤35% in sinus rhythm and resting heart rate ≥70 bpm despite guidelines-recommended treatment.<br>2. Start in patients with stable symptomatic HF (NYHA Class II–IV) who are already treated with maximal tolerated evidence-based doses of an ACE-I (or an ARB), a beta-blocker and an MRA. |
| **Contra-indications:**<br>1. Unstable cardiovascular conditions (acute coronary syndrome, stroke/TIA, severe hypotension).<br>2. Severe liver dysfunction or renal dysfunction (no evidence on safety or pharmacokinetics for creatinine clearance <15 mL/min).<br>3. Pregnancy or breastfeeding.<br>4. Known allergic reaction/other adverse reaction (drug-specific). |
| **Cautions/seek specialist advice:**<br>1. Severe (NYHA Class IV) HF.<br>2. Current or recent (<4 weeks) exacerbation of HF (e.g. hospital admission with worsening HF).<br>3. Resting heart rate <50 bpm during treatment.<br>4. Moderate liver dysfunction.<br>5. Chronic retinal diseases, including retinitis pigmentosa.<br>6. Drug interactions:<br>o To look out for (due to a potential risk of bradycardia and induction of long QT as a result of bradycardia):<br>• Verapamil, diltiazem (both should be discontinued).<br>• Beta-blocker.<br>• Digoxin.<br>• Amiodarone.<br>o To look out for (drugs being strong inhibitors of isoenzyme CYP3A4 cytochrome P450):<br>• Antifungal azoles (such as ketoconazole, itraconazole).<br>• Macrolide antibiotics (such as clarithromycin, erythromycin).<br>• HIV protease inhibitors (nelfinavir, ritonavir).<br>• Nefazodone. |
| **WHAT DOSE? - See Table 7.2** |
| Ivabradine: starting dose 5 *mg b.i.d.*, target dose 7.5 mg *b.i.d.* |
| **WHERE?** |
| • In the community in stable patients in NYHA Class II–III.<br>• Patients in NYHA Class IV or those with a recent HF exacerbation should be referred for specialist advice.<br>• Other exceptions–see 'Cautions/seek specialist advice'. |
| **HOW TO USE?** |
| • Start with a low dose (5 mg *b.i.d.*) (see Table 7.2). In patients over 75 years old, a lower starting dose of 2.5 mg *b.i.d.* can be used.<br>• Daily dose may be increased to 7.5 mg *b.i.d.*, decreased to 2.5 mg *b.i.d.* or stopped depending on the patient's resting heart rate. Double the dose not more frequently than at 2-week intervals (slower up-titration may be needed in some patients). Aim for target dose (see above) or, failing that, the highest tolerated dose based on resting heart rate. If the resting heart rate is between 50 and 60 bpm, the current dose should be maintained.<br>• Monitor heart rate, blood pressure, and clinical status.<br>• When to stop up-titration, reduce dose, stop treatment – see PROBLEM SOLVING.<br>• A specialist HF nurse may assist with education of the patient, monitoring resting heart rate, follow-up (in person or by telephone), and dose up-titration. |
| **PROBLEM SOLVING** |
| • Treatment must be reduced or stopped if the resting heart rate decreases persistently below 50 bpm or if symptoms of bradycardia occur<br>o Review need for other heart rate-slowing drugs or drugs interfering with ivabradine liver metabolism.<br>o Arrange electrocardiogram to exclude other than sinus bradycardia rhythm disturbances.<br>o Consider screening for secondary causes of bradyarrhythmias (e.g. thyroid dysfunction).<br>• If a patient develops persistent/continuous AF during the therapy with ivabradine, the drug should be stopped.<br>• Visual phenomena are usually transient, and disappear during the first few months of ivabradine treatment and are not associated with serious retinal dysfunction. However, if they result in the patient's discomfort, the discontinuation of ivabradine should be considered.<br>• In case of lactose or galactose intolerance (component of the ivabradine tablet), if symptoms occur, there may be a need to stop the drug. |
| **ADVICE TO PATIENT** |
| • Explain expected benefits (see WHY?)<br>o Treatment is given to prevent worsening of HF leading to hospital admission and to reduce the risk cardiovascular death.<br>• In order to detect a potential bradycardia, patients should be encouraged to measure and record his/her pulse on a regular basis.<br>• Advise patient to report side effects to the physician or HF nurse. Side effects due to symptomatic bradycardia: breathlessness, fatigue, syncope, dizziness; other side effects: luminous visual phenomena. |

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; *b.i.d.* = twice daily; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HIV = human immunodeficiency virus; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; TIA = transient ischaemic attack.

[a]The recommendations in this table represent expert opinion based upon relevant clinical trials (drugs, titration schedules, target doses, patient monitoring, treatment benefits, and reported adverse effects) and clinical experience.

**Web Table 9.1 Phase II and III clinical trials performed in patients with heart failure with mid-range ejection fraction and heart failure with preserved ejection fraction**

| Trial | Intervention | Major inclusion criteria | Mean follow-up | Primary endpoints |
|---|---|---|---|---|
| PEP-CHF[320] | Perindopril vs placebo. | LV wall motion index ≥1.4 (corresponding to LVEF ≥40%), symptomatic HF treated with diuretic, diastolic dysfunction in echocardiography, age ≥70 y. | 2.1 y | No difference in combined all-cause mortality or cardiovascular hospitalization (36% vs 37%, *P* =0.35). |
| I-PRESERVE [318] | Irbesartan vs placebo. | LVEF ≥45%, NYHA III–IV with corroborative evidence, or NYHA II with HF hospitalization in recent 6 months, age ≥60 y. | 4.1 y | No difference in combined all-cause mortality or HF hospitalization (24% vs 25%, *P* =0.54). |
| CHARM-Preserved[319] | Candesartan vs placebo. | LVEF >40%, NYHA II–IV, history of cardiac hospitalization. | 3.0 y | Trend towards a reduction in combined cardiovascular mortality or HF hospitalization by 11% (22% vs 24%, unadjusted *P* =0.12, adjusted *P* =0.051). |
| Aldo-DHF[330] | Spironolactone vs placebo. | LVEF ≥50%, NYHA II–III, peak $VO_2$ ≤25 mL/min/kg, diastolic dysfunction on echocardiography or atrial fibrillation, age ≥50 y. | 1.0 y | Reduction in E/e' by – 1.5 (*P* < 0.001)<br>No change in peak $VO_2$ (*P* =0.81). |
| TOPCAT[310] | Spironolactone vs placebo. | LVEF ≥45%, ≥1 HF sign, ≥1 HF symptom, HF hospitalization within recent 12 months, or BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL, age ≥50 y. | 3.3 y | No difference in combined cardiovascular death, aborted cardiac arrest, or HF hospitalization (19% vs 20%, *P* =0.14). |
| SENIORS[173] | Nebivolol vs placebo. | HF confirmed as HF hospitalization in recent 12 months and/or LVEF ≤35% in recent 6 months, age ≥70 y, 36% with LVEF >35%. | 1.8 y | Reduction in combined all-cause mortality or cardiovascular hospitalization by 14% (31% vs 35%, *P* =0.04). |
| DIG-PEF[323] | Digoxin vs placebo. | HF with LVEF >45%, sinus rhythm. | 3.1 y | No difference in combined HF mortality or HF hospitalization (21% vs 24%, *P* =0.14) |
| PARAMOUNT[309] | Sacubitril/ valsartan vs valsartan. | HF with LVEF ≥45%, NYHA II-III, NT-proBNP >400 pg/mL. | 12 w | Reduction in NT-proBNP: ratio of change sacubitril/ valsartan 0.77, 95% CI 0.64–0.92 (*P* =0.005). |
| RELAX[311] | Sildenafil vs placebo. | HF with LVEF ≥45%, NYHA II-IV, peak $VO_2$ <60% of reference values, NT-proBNP >400 pg/mL or high LV filling pressures. | 24 w | No change in peak $VO_2$ (*P* =0.90). |

Aldo-DHF = Aldosterone Receptor Blockade in Diastolic Heart Failure; BNP = B-type natriuretic peptide; CHARM-Preserved = Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality; DIG-PEF = ancillary Digitalis Investigation Group trial; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Ejection Fraction Study; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NT-proBNP = N-terminal pro-B type natriuretic peptide; NYHA = New York Heart Association; PARAMOUNT = LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction; Peak $VO_2$ = peak oxygen uptake; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; RELAX = Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; w = week; y = year.

**Web Table 10.1 Assessment of stroke risk in patients with atrial fibrillation**

| $CHA_2DS_2$-VASc | |
|---|---|
| Congestive HF or LV dysfunction | 1 |
| Hypertension | 1 |
| Age ≥75 years | 2 |
| Diabetes mellitus | 1 |
| Stroke, transient ischaemic attack, or thrombo-embolism | 2 |
| Vascular disease (previous myocardial infarction, peripheral artery disease, or aortic plaque) | 1 |
| Age 65–74 years | 1 |
| Sex category (i.e. female sex) | 1 |
| Maximum score | 9 |
| $CHA_2DS_2$-VASc score = 0 for males, or 1 in females: no antithrombotic therapy. | |
| $CHA_2DS_2$-VASc score = 1 in males or 2 in females: consider oral anticoagulation. | |
| $CHA_2DS_2$-VASc score ≥2 in males or ≥3 in females: recommend oral anticoagulation. | |

$CHA_2DS_2$-VASc = Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category (female); HF = heart failure; LV = left ventricular.

**Web Table 10.2 Assessment of bleeding risk in patients with atrial fibrillation**

| HAS-BLED | |
|---|---|
| Hypertension (systolic blood pressure >160 mmHg). | 1 |
| Abnormal renal and liver function (1 point each). | 1 or 2 |
| Stroke | 1 |
| Bleeding tendency or predisposition. | 1 |
| Labile international normalized ratio (if on warfarin). | 1 |
| Elderly (e.g. age >65 years). | 1 |
| Drugs (e.g. concomitant aspirin, NSAID) or excess alcohol (1 point each). | 1 or 2 |
| Maximum score | 9 |
| A HAS-BLED score ≥3 suggests that caution is warranted when prescribing oral anticoagulation that regular review is recommended and that the reversible bleeding risk factors are addressed. | |

HAS-BLED = Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly (1 point each); NSAID = non-steroidal anti-inflammatory drug.