ACUTE HEART FAILURE
Supporting information

This guideline has been prepared with reference to the following:

Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895-e1032

https://www.ahajournals.org/doi/10.1161/CIR.0000000000001063

NICE. Acute heart failure: diagnosis and management. 2021. NICE. London

https://www.nice.org.uk/guidance/cg187

McDonagh TA, Metra M, Adamo M et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599-726

https://academic.oup.com/eurheartj/article/42/36/3599/6358045

NICE. Chronic heart failure in adults: diagnosis and management. 2018. NICE. London

https://www.nice.org.uk/guidance/ng106

Immediate treatment

Administration of oxygen improves the clinical outcome in patients with acute pulmonary oedema?

A 2019 systematic review of RCTs concluded that non-invasive positive pressure ventilation (NPPV) improves outcomes such as hospital mortality and intubation rates. NPPV is a safe intervention with similar adverse event rates to standard medical care alone (Berbenetz, 2019). This review of 24 RCTs found that compared with standard medical care, NPPV may reduce hospital mortality (risk ratio (RR) 0.65, 95% confidence interval (CI) 0.51 to 0.82). NPPV probably reduces endotracheal intubation rates (RR 0.49, 95% CI 0.38 to 0.62). There is probably little or no difference in acute myocardial infarction incidence with NPPV compared to SMC for acute cardiogenic pulmonary oedema (RR 1.03, 95% CI 0.91 to 1.16). We are uncertain as to whether NPPV increases hospital length of stay (mean difference (MD) -0.31 days, 95% CI -1.23 to 0.61). Adverse events were generally similar between NPPV and standard medical care groups, but evidence was of low quality.

Berbenetz N, Wang Y, Brown J et al. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. Cochrane Database Syst Rev. 2019 Apr 5;4:CD005351
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005351.pub4/full

Evidence level: I

Intravenous furosemide improves the clinical outcome in patients with acute pulmonary oedema?

A 2021 RCT concluded that nubulised furosemide was more beneficial than intravenous furosemide (Barzegari, 2021). This study (80 patients) found that whilst nubulised furosemide was not superior to intravenous furosemide in reducing dyspnea and crackles in patients with acute pulmonary edema, it did significantly improve respiratory rate and arterial blood oxygen and resulted in less hemodynamic changes.

An updated meta-analysis of 10 trials in a total of 564 patients (Amer, 2012) found that, when administered as a continuous infusion, furosemide resulted in greater diuresis (WMD, -240.54 mL/24 hours/100 mg furosemide; 95% CI -462.42 to -18.66) and reduction in total body weight (WMD, -0.78 kg; 95% CI, -1.54 to -0.03), than when administered in intermittent boluses. Urinary sodium excretion (WMD, -20.26 mmol/24 hours; 95% CI, -60.48 to 19.96) and duration of hospital stay (WMD, 0.99 days; 95% CI, -2.08 to 4.06) were not different between the 2 groups.

Amer M, Adomaityte J, Qayyum R. Continuous infusion versus intermittent bolus furosemide in ADHF: an updated meta-analysis of randomized control trials. J Hosp Med 2012;7:270-5

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Barzegari H, Khavanin A, Delirrooyfard A et al. Intravenous furosemide vs nebulized furosemide in patients with pulmonary edema: A randomized controlled trial. Health Sci Rep. 2021;4:e235
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7808786/

Evidence Level: I

Intravenous injection of furosemide at a rate exceeding 4 mg per minute can be hazardous?
Infusion rates exceeding 4 mg per minute carry a risk of ototoxicity (Gallagher, 1979, Schwartz, 1979). In 29 cases reported to the FDA in the U.S. (Gallagher, 1979), total doses resulting in hearing loss ranged from 40 mg to 21.6 g, but damage was only reported to occur when the manufacturer's recommended iv rate of 4 mg per minute was exceeded. Damage is also more likely to occur in patients with impaired renal function (Schwartz, 1970).

Gallagher KL, Jones JK . Furosemide-induced ototoxicity. Ann Intern Med 1979; 91:744-5

Schwartz GH, David DS, Riggio RR, et al. Ototoxicity induced by furosemide. N Engl J Med 1970;282:1413-14

Evidence Level: V

Slow intravenous injection of diamorphine improves the clinical outcome in patients with acute pulmonary oedema?
Morphine "reduces anxiety, reduces adrenergic vasoconstrictor stimuli to the arteriolar and venous beds, and thereby helps to break a vicious cycle" (Fauci, 1998). The same author advises that naloxone should be available in case respiratory depression occurs. Hoffman (1987) found in a series of 57 patients that nitroglycerin was superior to morphine as a vasodilating agent whilst avoiding respiratory depression. In a review of 332 cases of high-altitude pulmonary oedema (Singh, 1965), the authors found that the principal effect of morphine was in restoring laboured breathing to normal. This laboured breathing resulted in negative intrathoracic pressures and a collapsing effect on alveolar vessels, impeding oxygenation of the blood. A rapid improvement with 100% oxygen inhalation was seen following administration of 15-20 mg iv of morphine, repeated after half an hour if necessary.
The use of morphine and its analogues is recommended in current European guidelines (Anon, 2012).

Anon. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. The Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2012;33: 1787-847
http://eurheartj.oxfordjournals.org/content/33/14/1787.long

Fauci AS, Braunwald E, Isselbacher KJ, et al. Harrison's Principles of internal medicine, 14th ed. New York: Mcgraw-Hill, 1998. p1297

Hoffman JR, Reynolds S. Comparison of nitroglycerin, morphine and furosemide in treatment of presumed pre-hospital pulmonary edema. Chest 1987; 92:586-93
http://journal.publications.chestnet.org/data/Journals/CHEST/21568/586.pdf

Singh I, Kapila CC, Khanna PK, et al. High-altitude pulmonary oedema. Lancet 1965;i:229-34

Evidence Level: V

Elderly or frail patients with acute pulmonary oedema are more sensitive to diamorphine than younger patients?
Martindale states that "doses may be reduced by half for elderly or frail patients" without providing any reference to support the suggestion (Sweetman, 2007). Brocklehurst (1992) repeats the advice and quotes Dodson (1988) in explaining that smaller doses of opioids are needed in older patients to achieve the required effect, whilst respiratory depression is more likely than in the younger patient.

Brocklehurst JC, Tallis RC, Fillit HM. Textbook of geriatric medicine and gerontology, 4th ed. Edinburgh: Churchill Livingstone, 1992. p955

Dodson ME. Modifications of general anaesthesia for the aged. In: Davenport HT, (ed) Anaesthesia and the aged patient. Oxford: Blackwell, 1988. p204-30

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Sweetman SC (ed). Martindale: the complete drug reference, 35th ed. London: Pharmaceutical Press, 2007

Evidence Level: V

Infusion of glyceryl trinitrate improves the clinical outcome in patients with severe acute pulmonary oedema provided systolic blood pressure exceeds 100 mmHg?

A narrative review (Schneider, 1991) describes nitrates as "drugs of first choice in patients with acute heart failure" and considers them safe to use when systolic blood pressure exceeds 95 mmHg. The authors treat acute pulmonary oedema with sublingual glyceryl trinitrate, reserving the i.v. route for prolonged acute heart failure. A randomised trial (Cotter, 1998) compared high-dose intravenous isosorbide dinitrate plus low-dose furosemide with low-dose isosorbide dinitrate and high-dose furosemide. Seven of 52 (13%) patients in the high-dose nitrates group needed mechanical ventilation, compared to 21 of 52 (40%) in the low-dose nitrates group.

A retrospective analysis of observational data from the Acute Decompensated Heart Failure National Registry (ADHERE) involved 65180 patient episodes (Abraham, 2005). Patients receiving nitroglycerin or nesiritide had lower in-hospital mortality than those receiving dobutamine or milrinone (RR 0.69 (95% CI 0.53-0.89, p</= 0.005).

Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005;46:57-64
http://www.sciencedirect.com/science/article/pii/S0735109705008557

Cotter G, Metzkor E, Kaluski E, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet 1998;351:389-93

Schneider W, Bussmann WD, Hartmann A, et al. Nitrate therapy in heart failure. Cardiology 1991;79:s5-13

Evidence Level: III

Intravenous dobutamine in patients with severe acute pulmonary oedema whose systolic blood pressure is <100 mmHg improves the clinical outcome?

Dobutamine increases contractility and reduces peripheral vascular resistance and left ventricular end-diastolic pressure. It has a place in patients not responding to standard therapy and who demonstrate significant systolic dysfunction (Felker, 2001*).* Intermittent dobutamine therapy increased exercise duration and heart-rate response (in a randomised comparison with placebo) in 20 patients with refractory heart failure (Erlemeier, 1992), and also in a trial of 24 patients with advanced congestive heart failure (Ferroni, 1996). A subgroup meta-analysis of data from the Flolan International Randomized Survival Trial (FIRST) (O'Connor, 1999) indicates that intravenous dobutamine is associated with increased mortality at 6 months (70.5% vs 37.1%; P = .0001) when compared to a control group not receiving dobutamine. Dobutamine emerged as an independent risk factor for death (mostly from ventricular arrhythmias) after adjusting for baseline differences.

An overview of RCTs in this area (Teerlink, 2005) acknowledges that survival benefit is difficult to prove in the absence of placebo-controlled trials, but also that some patients have few other options.

Erlemeier HH, Kupper W, Bleifeld W. Intermittent infusion of dobutamine in the therapy of severe congestive heart failure: long-term effects and lack of tolerance. Cardiovasc Drugs Ther 1992;6:391-8

Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. Am Heart J 2001;142:393-401

Ferroni C, Fraticelli A, Paciaroni E. Intermittent dobutamine therapy in patients with advanced congestive heart failure. Arch Gerontol Geriatr 1996;23:313-27

O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138:78-86

Teerlink JR. Overview of randomized clinical trials in acute heart failure syndromes. Am J Cardiol 2005;96(Suppl):59G-67G

Evidence Level: IV; III (Observational analysis of RCT data) for O'Connor

Subsequent management

Reducing daily salt intake by avoiding added salt and salty food improves the clinical outcome in acute heart failure?

In a 2023 meta-analysis of RCTs, salt restriction was not associated with fewer deaths or hospitalizations in patients with heart failure (Colin-Ramirez, 2023). Seventeen RCTs were identified (834 and 871 patients in intervention and control groups, respectively). Salt restriction did not reduce the risk of all-cause death (odds ratio, 0.95 [95% CI, 0.58 to 1.58]), hospitalization (odds ratio, 0.84 [95% CI, 0.62 to 1.13]), or the composite of death/hospitalization (odds ratio, 0.88 [95% CI, 0.63 to 1.23]).

A 2016 review found that current evidence does not support the restriction of salt as a means to improve outcomes in heart failure (Colin-Ramirez, 2016). A lack of strong evidence has not prevented some guideline issuing bodies from recommending restricted salt dietary intake. The Canadian Cardiovascular Society, the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand all recommend less than 2000mg of sodium intake. The Heart Failure Society of America recommend less than 3000mg. NICE however, have not issued any recommendations (Colin-Ramirez, 2016).

Colin-Ramirez E, Ezekowitz JA. Salt in the diet in patients with heart failure: what to recommend. Curr Opin Cardiol. 2016;31:196-203

Colin-Ramirez E, Sepehrvand N, Rathwel S et al. Sodium Restriction in Patients With Heart Failure: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Circ Heart Fail. 2023;16:e009879

Evidence Level: I

Excessive fluid intake in patients with cardiac failure interferes with the beneficial effects of diuretic therapy?

A 2016 meta analysis of six RCTs could found no benefit from fluid restriction with regard to hospitalisation and mortality. The authors commented that “considering that the quality of life may be worsened by the sense of intense thirst that a restricted water intake can entail, in our opinion, the partial deprivation of water in the diet should be reserved only to selected cases of heart failure (particularly, the cases characterized by widespread edema and/or ascites), for relatively short periods”.

De Vecchis R, Baldi C, Cioppa C et al. Effects of limiting fluid intake on clinical and laboratory outcomes in patients with heart failure. Results of a meta-analysis of randomized controlled trials. Herz. 2016;41:63-75

Evidence Level: I

An extra 40 mg furosemide daily is an appropriate first step in patients with cardiac failure who are already taking oral furosemide?

A small, randomised study of 10 patients (Cowley, 1986) found a higher dose of furosemide in those already taking 40mg/d more effective than adding captopril to the regimen. Dyspnoea, fatigue, general well-being and exercise tolerance were all improved. A study of 115 hospitalised patients (Exaire, 1975) found that, although some required 80-120 mg/d, a high proportion (62%) were eventually controlled on only 20 mg/d, underlining the need for periodic re-evaluation of diuretic requirements of patients on maintenance therapy.

Cowley AJ, Stainer K, Wynne RD, et al. Symptomatic assessment of patients with heart failure: double-blind comparison of increasing doses of diuretics and captopril in moderate heart failure. Lancet 1986; 2:770-2

Exaire JE, Villalpando J, Hamdan G, et al. Dosage titration with furosemide in congestive heart failure patients. Angiology 1975;26:665-70

Evidence Level: II

Furosemide should be given intravenously rather than orally in patients who have gross peripheral oedema (above the knees)?

Absorption of oral furosemide can be erratic, especially in patients with heart failure, and doses higher than 50 mg (usually required to reduce gross oedema*)* should be given by slow intravenous infusion

(Sweetman, 2002) in order to circumvent this. A case series of 35 patients (Gerlag, 1988) found slow intravenous infusion of high-dose furosemide reduced gross oedema by 3-10kg/d, reduced body weight by 3-22kg and improved the NYHA classification in all patients. Oral administration was resumed when normal hydration was attained. In a series of 10 patients (Lawson, 1978) who had failed to respond to 120mg of oral furosemide, iv infusion rates of 4-16mg/h were used to achieve peak sodium excretion rates of 5.5 mmol/min. This was associated with plasma furosemide concentrations of 0.5 mg/l, compared with 10mg/l to achieve the same effect from an 80mg i.v. bolus dose.

Gerlag PG, van Meijel JJ. High-dose furosemide in the treatment of refractory congestive heart failure. Arch Intern Med 1988;148:286-91

Lawson DH, Gray JM, Henry DA, et al. Continuous infusion of frusemide in refractory oedema. BMJ 1978; ii:476 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1606785/pdf/brmedj00139-0028a.pdf

Sweetman SC (ed). Martindale: the complete drug reference, 33rd ed. London: Pharmaceutical Press, 2002. p895

Evidence Level: V

A rate of weight reduction exceeding 0.5 kg per day may be hazardous in patients receiving intravenous diuretic therapy?
Weight reduction exceeding 0.5 kg per day may occur with the over-aggressive use of diuretics and could induce severe ventricular arrhythmias due to depletion of potassium and magnesium (Bigger, 1987). A randomised crossover trial in 10 patients with ischaemic heart disease (Stewart, 1985) compared potassium losing and potassium sparing diuretic treatments. It was found that the potassium losing treatments resulted in increased ventricular instability even though they caused relatively mild hypokalaemia (3.3mmol/ v 4.3mmol/l for the sparing treatment).

Bigger JT. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. Circulation 1987;75(Suppl IV):IV-28-IV-35

Stewart DE, Ikram H, Espiner EA, et al. Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease. Br Heart J 1985;54:290-7 http://heart.bmj.com/content/54/3/290.long

Evidence Level: III

Dividing the daily dose of loop diuretic and giving part of it in the early afternoon can afford symptomatic relief in patients who have troublesome nocturnal dyspnoea?
Furosemide's effects are evident within 30 minutes to 1 hour after a dose by mouth, peak at 1 to 2 hours, and last for about 4 to 6 hours (Sweetman, 2002). As acute pulmonary oedema causing dyspnoea is known to respond to loop diuretics (Weatherall, 1996), it would seem logical that part of the dose given later in the day would help to prevent nocturnal attacks. In a small series of 20 patients suffering from "cardiac asthma" (Mehta, 1986), 15 responded to their diuretic dose being split (furosemide 40mg orally at 5.00 pm, furosemide 20mg iv at 7.00 pm) by sleeping well throughout the night.

Mehta MR, Garg MK. "Evening diuretics". J Assoc Physicians India 1986;34:304-5

Sweetman SC (ed). Martindale: the extra pharmacopoeia, 33rd ed. London: Royal Pharmaceutical Society, 2002. p895

Weatherall DJ, Ledingham JG, Warrell DA. Oxford textbook of medicine. 3rd ed. Oxford: Oxford University Press, 1996. p2164

Evidence Level: V

Routine use of an ACE inhibitor without the need for prior echocardiography carries no unacceptable risk in patients who have no clinical suspicion of significant mitral/aortic stenosis or hypertrophic cardiomyopathy, and whose renal function is not seriously impaired (plasma creatinine <300 micromol/litre)?
The North of England Guidelines on this subject (Eccles, 1998) recommend that echocardiography or radionuclide measurement should be used (where available) to evaluate left ventricular function in all

patients with suspected heart failure who are being considered for ACE inhibitor treatment. If these facilities are not available, the recommendation is to use an algorithm with questions based on the patient's past medical history, response to diuretics, chest x-ray and ECG findings. Diagnosis by this method is estimated to be accurate in only 50% of cases. The routine use of echocardiography is also advocated in an AHCPR guideline (Konstam, 1994).

Eccles M, Freemantle N, Mason J. North of England evidence based development project: guideline for angiotensin converting enzyme inhibitors in primary care management of adults with symptomatic heart failure. BMJ 1998;316:1369-75
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1113074/

Konstam M, Dracup K, Baker D, et al. Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction. Clinical Practice Guideline 11. Rockville: Agency for Health Care Policy and Research, 1994.

Evidence Level: V

Routine addition of a potassium-sparing agent (amiloride) to existing loop diuretic therapy (to conserve potassium provided plasma creatinine is <150 micromol/litre) is necessary in patients in whom an ACE inhibitor is contraindicated or not tolerated?
Hypokalaemia, which may result from vigorous use of diuretics, can precipitate or aggravate ventricular arrhythmias in patients with heart failure. For this reason, potassium should be replaced (or its loss guarded against). No conclusive data exists to determine whether routine administration of potassium-sparing diuretics reduces serious morbidity or mortality in these patients (Braunwald, 1997). Current advice is based largely on studies in hypertensive patients, in whom cardiac events were more common when diuretics were given without additional potassium sparing agents (Siscovick, 1994). A study of 49 patients with heart failure who were taking furosemide (Davidson, 1978) found that plasma levels of potassium rose in response to amiloride given over 5 months, but not total body or red cell levels, suggesting that this group of patients had not suffered significant depletion of body potassium.

Braunwald E. Heart disease: a textbook of cardiovascular medicine, 5th ed. Philadelphia: Saunders, 1997. p479

Davidson C, Burkinshaw L, Morgan DB. The effects of potassium supplements, spironolactone or amiloride on the potassium status of patients with heart failure. Postgrad Med J 1978; 54:405-9
http://pmj.bmj.com/content/54/632/405.long

Siscovick DS, Raghunathan TE, Psaty BM, et al. Diuretic therapy for hypertension and the risk of primary cardiac arrest. N Engl J Med 1994; 330:1852-7
http://www.nejm.org/doi/full/10.1056/NEJM199406303302603#t=articleTop

Evidence Level: V

If ACE inhibitor not tolerated, Candesartan (angiotensin 2 antagonist) should be substituted?
The CHARM-Alternative trial (Granger, 2003) randomly assigned 2028 patients intolerant of ACE inhibitors to either placebo (n=1015) or candesartan 32 mg daily (n=1013). During a median follow-up of 33.7 months, combined end points of cardiovascular death or hospital admission for cardiac failure were experienced by 334 (33%) of patients in the candesartan group vs 406 (40%) of the control group (RR 0.77; 95% CI 0.67-0.89, p<0.0001, NNT 14).

Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003;362:772-6

Evidence Level: II

Bisoprolol 1.25 mg/d is of benefit if started before discharge and there are no contraindications and systolic blood pressure is >100mmHg?
A multicentre double-blind randomised controlled trial in 2647 patients (Anon, 1999), of bisoprolol 1.25 mg/d (progressively increased to a maximum of 10 mg/d), was stopped early as the treatment group showed a significant mortality benefit (11.8% vs 17.3% with a hazard ratio of 0.66; 95% CI 0.54-0.81, p<0.0001). This beneficial effect, which appears to be related to the preservation of left ventricular function (Lechat, 1997), has not yet been established in patients with severe class IV symptoms.

A meta-analysis of 23 RCTs (Abdulla, 2006) showed significantly reduced all cause mortality with beta-blocker treatment compared to placebo (OR 0.69; 95% CI 0.59 – 0.82).

Abdulla J, Kober L, Christensen E, et al. Effect of beta-blocker therapy on functional status in patients with heart failure: a meta-analysis. Eur J Heart Fail 2006;8:522-31
http://onlinelibrary.wiley.com/doi/10.1016/j.ejheart.2005.10.012/full

Anon. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. CIBIS-II Investigators and Committees. Lancet 1999;353:9-13
http://columbiamedicine.org/education/r/Cardiology/CHF/Beta-Blocker/CIBIS-II.pdf

Lechat P, Escolano S, Golmard JL, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1997;96:2197-2205
http://circ.ahajournals.org/content/96/7/2197.long

Evidence Level: I

Are angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARB), beta blockers (BB) or mineralocorticoid receptor antagonists (MRA) of benefit for patients with heart failure with preserved ejection fraction (HFpEF)?

A 2021 review found that ACE inhibitors and ARBs did not improve mortality and HF hospitalization in patients with HFpEF except for a weak positive result for HF hospitalization by candesartan (Kim, 2021). The same review also failed to find firm evidence that mineralocorticoid receptor antagonists were of benefit.

In a meta-analysis of 11 RCTs, BBs did not improve prognosis in HFpEF (Cleland, 2018). Another recent meta-analysis revealed that BB had no clear benefit on the severity of HFpEF but it was associated with favorable outcomes in HFpEF with coronary artery disease or atrial fibrillation (Fukuta, 2021).

A 2025 systematic review concluded that MRAs improve echocardiographic parameters of diastolic function and BP control; however, this did not translate into clinical outcomes of improved functional capacity or quality of life (Zaheen, 2025). Meta-analysis revealed a significant benefit of MRA use compared to the control in decreasing E/e' (standardised mean difference [SMD] -0.21; 95% CI: -0.33 to -0.10), with greater improvement seen with longer duration of treatment. A substantial reduction in systolic blood pressure (SMD -0.27; 95% CI: -0.53 to -0.02) and diastolic blood pressure (SMD -0.18; 95% CI: -0.32 to -0.04) was also noted. There was no significant difference in the 6 min walk distance, peak exercise capacity, or quality-of-life measures. Adverse events such as hyperkalaemia and worsening renal function were frequently reported in the MRA group.

Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39:26-35

Fukuta H, Goto T, Wakami K et al. Effect of beta-blockers on heart failure severity in patients with heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Heart Fail Rev. 2021;26:165-71

Kim MN & Park SM. Current Status of Pharmacologic and Nonpharmacologic Therapy in Heart Failure with Preserved Ejection Fraction. Heart Fail Clin. 2021;17:463-82

Zaheen M, Ferdous F, Amarasekera AT et al. Mineralocorticoid Receptor Antagonists in Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-Analysis. J Clin Med. 2025;14:3598
https://pmc.ncbi.nlm.nih.gov/articles/PMC12112577/

Evidence Level: I

Are sodium–glucose cotransporter-2 inhibitors (SGL2i) of benefit for patients with heart failure with preserved ejection fraction (HFpEF)?

A 2022 meta-analysis evaluated the effect of SGL2i vs. placebo on all-cause mortality, cardiovascular mortality, and hospitalization from heart failure (Zou, 2022). The meta-analysis included three RCTs in patients with HFpEF (n = 8,610). The interventions were empagliflozin, canagliflozin, and sotagliflozin; patients were followed for six to nine months. The meta-analysis of all three studies showed that, compared with placebo, SGL2i inhibitors decreased hospitalization from heart failure (relative risk =

0.72; 95% CI 0.5 to 0.96) but had no effect on all-cause or cardiovascular mortality. A 2025 meta-analysis of 9 RCTs came to the same conclusion (Minisy, 2025).

Minisy MM & Abdelaziz A. The role of SGLT 2 inhibitors in heart failure with preserved ejection fraction (HFpEF): a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2025;25:765 https://pmc.ncbi.nlm.nih.gov/articles/PMC12557931/

Zou X, Shi Q, Vandvik PO, et al. Sodium-glucose cotransporter-2 inhibitors in patients with heart failure: a systematic review and meta-analysis. Ann Intern Med. 2022; 175:851–61

Evidence Level: I

Discharge and follow-up

Prolonged rest can be counter-productive, so patients should be mobilised once they are no longer short of breath at rest?

Although rest is indicated in acute heart failure or exacerbations of chronic heart failure, prolonged rest is not encouraged in stable chronic heart failure (LeJemtel, 1998). Deconditioning related to muscular inactivity and decreased metabolic vascular dilatation is a major factor in reducing exercise performance as heart failure progresses (Mancini, 1987).

A 2024 systematic review of observational studies found that early mobilisation may result in a large reduction in the readmission rate compared with that of the control (two studies, 283 participants: odds ratio 0.25, 95 % confidence interval 0.14 to 0.42) [Okamura, 2024]. The authors of this review concluded that early mobilisation, defined as protocol-based interventions or walking within 3 days of admission, may be associated with a low readmission rate in patients with acute HF.

LeJemtel TH, Sonnenblick EH, Frishman WH. Diagnosis and management of heart failure. In: Alexander RW, et al (eds.) Hurst's The heart, arteries and veins, 9th ed. New York: McGraw-Hill, 1998. p750

Mancini DM, Davis L, Wexler JP, et al. Dependence of enhanced maximal exercise performance on increased peak skeletal muscle perfusion during long-term captopril therapy in heart failure. J Am Coll Cardiol 1987;10:845-50

Okamura M, Kataoka Y, Taito S et al. Early mobilization for acute heart failure: A scoping and a systematic review. J Cardiol. 2024;83:91-9

Evidence Level: V

If patient stable on ACE inhibitor and diuretics, bisoprolol 1.25mg daily (titrated up in 1.25mg increments at two-weekly intervals to a maximum of 10mg) is beneficial in appropriate patients?

CIBIS-II (Anon, 1999) was a European, multicentre, double-blind, randomised, placebo-controlled trial of 2647 symptomatic (NYHA class III and IV) heart failure patients receiving standard treatment with ACE inhibitors and diuretics. Patients randomised to treatment with bisoprolol 1.25mg daily (n=1327), increasing to a maximum of 10mg, showed a total reduction in mortality of nearly 34% and a reduction in sudden death of more than 40% compared with placebo (n=1320). The authors caution that results should not be extrapolated to patients with severe class IV symptoms and recent instability.

A meta-analysis of 18 trials in a total of 8119 patients (Whorlow, 2000) found a RR benefit of β–blockers vs placebo of 0.71 (95% CI 0.52-0.96) in NYHA class IV patients.

On the basis of the available evidence, all patients with chronic, stable, mild to moderate symptomatic heart failure with depressed left ventricular function should be treated with β–blockers (Foody, 2002; Pritchett, 2002; Shibata, 2001). It is possible that different heart failure population subgroups may have different responses to beta-blocker therapy (Domanski, 2003).

In a population-based cohort study of 11,942 patients (Sin, 2002), beta-blocker therapy was associated with substantial reductions in all-cause mortality (hazard ratio [HR] 0.72; 95% CI 0.65-0.80), mortality due to heart failure (HR 0.65; 95% CI 0.47-0.90) and hospitalisations for heart failure (HR 0.82; 95% CI 0.74-0.92).

A meta-analysis of 18 RCTs in a total of 928 patients (Faris, 2002) found reduced mortality compared to placebo (OR 0.25; 95% CI 0.07-0.84; P=0.03).

Secondary analysis of data from 3164 patients in the ATLAS study (Majumdar, 2004) found that patients receiving high-dose ACE inhibitors plus beta-blockers plus digoxin for 1 year had 12% fewer deaths and hospitalisations than patients receiving low-dose ACE inhibitors alone.

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Evidence Level: I

Last amended November 2025
Last reviewed January 2026