

# Updates in heart failure

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## ABSTRACT

This review provides a contemporary overview of HF management and highlights the key studies which have informed recent European HF guidelines.

### Introduction

In the UK, heart failure (HF) is the leading cause for hospital admission for those over 65 years of age and 21% of patients admitted with HF are readmitted within a month of discharge.<sup>1,2</sup> HF is a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.<sup>3,4</sup>

### Chronic HF

Patients with chronic HF suffer from the clinical syndrome of HF, but do not require urgent hospital attendance or admission. The National Institute for Health and Care Excellence (NICE) have produced clear guidelines regarding the investigation of suspected chronic heart failure (Fig 1). Patients with suspected heart failure should have NTpro-BNP testing performed. If NTproBNP is >400 ng/l, the patient should be referred for HF specialist assessment along a 2-week (NTproBNP >2,000 ng/l) or 6-week (NTproBNP 400–2,000 ng/l) diagnostic pathway.<sup>1</sup> Marked NT-proBNP elevation is related to poorer prognosis and HF assessment is urgent for these patients.<sup>1,5</sup> Specialist HF review informed by echocardiography is required to facilitate aetiological investigation and initiation of guideline directed medical therapy (GDMT) in tandem.<sup>4</sup>

### Classification of HF

In the context of a clinically congruent syndrome, assessment of left ventricular ejection fraction (LVEF) facilitates classification of HF into three groups:

- > heart failure with reduced ejection fraction (HFrEF) – LVEF ≤ 40%
- > heart failure with mildly reduced ejection fraction (HFmrEF) – LVEF 41–49% (a group now recognised to include a large

population of patients with improved LVEF following HF treatment)

- > heart failure with preserved ejection fraction (HFpEF) – LVEF ≥ 50%.

Treatment decisions depend on categorisation by LVEF.<sup>4</sup> Recovery of LV function is not an indication to withdraw HFrEF treatment.<sup>5</sup>

### Pharmacological management of HF with a reduced ejection fraction

There are currently four cardinal pharmacological treatments for HFrEF. The first is renin–angiotensin–aldosterone system inhibitors (RAASi), which include ACE-inhibitors (ACE-I), angiotensin receptor blockers (ARB) and angiotensin receptor/neprilysin inhibitors (ARNI); the other three are beta blockers, mineralocorticoid receptor antagonists (MRAs) and sodium glucose cotransporter-2 inhibitors (SGLT2i) (Fig 2). The ESC 2021 HF guidelines removed the

### Key points

Where there is a clinical suspicion of heart failure (HF), utilise NT-proBNP measurement followed by echocardiography to triage, diagnose, classify, and appropriately refer.

HF is classified by left ventricular ejection fraction (LVEF), which in turn guides management: HF with reduced EF (HFrEF, ≤40%), HF with mildly reduced EF (HFmrEF, 41–49%) and HF with preserved EF (HFpEF, ≥50%).

Beta blockers, ACE-inhibitors (ACE-I)/angiotensin II receptor blockers (ARB)/angiotensin II receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium glucose co-transporter-2 (SGLT-2) inhibitors are the ‘four pillars’ of HF pharmacotherapy for reduced ejection fraction.

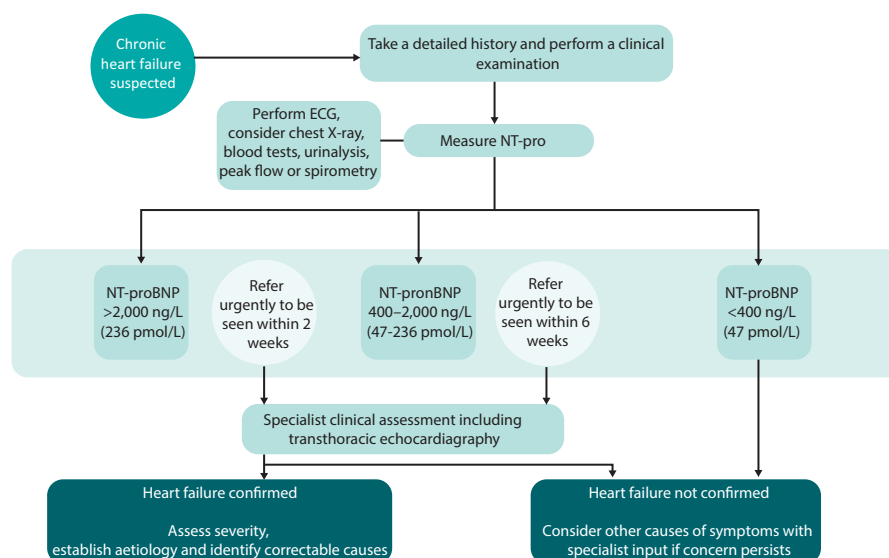
SGLT-2 inhibitors are the first drug class to demonstrate effectiveness in terms of reduced HF hospitalisation rates across the EF spectrum.

All patients admitted with acute HF should be reviewed by specialist HF services within 24 hrs to investigate aetiology, guide offloading strategies, and initiate prognostic HF therapy.

**KEYWORDS:** heart failure, guidelines, pharmacotherapy, device therapy, revascularisation

**DOI:**10.7861/clinmed.2023-2023-23.5.Cardio1

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**Fig 1. NICE guidelines summarising the investigation of suspected chronic heart failure.** This is a summary of the NICE recommendations on tests to offer to diagnose chronic heart failure from its guideline on chronic heart failure.<sup>1</sup> The guideline also covers management.

prescribed sequence of HF pharmacotherapy initiation in favour of a more pragmatic patient-centred approach; the choice of sequence is patient factor dependent. Treatment with these each of these ‘four pillars’ has been shown to extend lives, reduce HF hospitalisation and improve quality of life for patients with HFrEF.<sup>4</sup>

The recent addition of the ‘fourth pillar’, SGLT2 inhibition, to medical therapy for patients with HFrEF has been shown to significantly reduce cardiovascular death and hospitalisation for HF.<sup>6,7</sup> Meta-analysis of the EMPEROR-Reduced and DAPA-HF trials estimates that addition of SGLT2 inhibition to standard HF therapy confers a 13% reduction in all-cause mortality and a 25% decrease in the composite of recurrent hospitalisations for heart failure or cardiovascular death.<sup>8</sup>

Moreover, beneficial treatment effects are seen within days of initiation.<sup>9</sup> SGLT2 inhibitors require no dose titration once initiated and are well tolerated.<sup>10</sup> Safety concerns raised in early trials regarding increased rates lower limb amputation and Fournier’s gangrene have not been borne out in subsequent work.<sup>10,11</sup> RCT data suggests that mycotic genital infection is the only consistently reported side effect of SGLT2 inhibition.<sup>10</sup> Post-licensing pharmacovigilance data and meta-analyses have, however, suggested a stronger association between SGLT2 inhibition and euglycaemic diabetic ketoacidosis than for other diabetic medications.<sup>10</sup> Thus, omission of SGLT2 inhibitors in the setting of an intercurrent illness causing reduced oral intake is advised to reduce risk of ketoacidosis. Following recovery SGLT2 inhibitors can be restarted after 24–48 hours of normal eating.<sup>12</sup>

PARADIGM-HF demonstrated that for patients with HFrEF, use of ARNI as compared with the ACE-I enalapril resulted in a better quality of life, less HF hospitalisation and lower all-cause mortality over more than 2 years of follow up.<sup>13</sup> Subsequent studies have demonstrated that initiation of ARNI is safe in both patients hospitalised for HFrEF and those who are ACEi/ARB naïve.<sup>14,15</sup> Rates of hyperkalaemia and worsening renal function, both of which can limit HF GDMT optimisation, were lower with sacubitril–valsartan compared to ACE inhibitors.<sup>13</sup> Sacubitril–valsartan is however associated with increased rates of symptomatic hypotension,

and this can be treatment limiting.<sup>13</sup> Treatment with ARNI should be considered for patients with HF, NYHA II–IV symptoms, and LVEF <35%. Existing ACE-I therapy should be discontinued prior to ARNI initiation, with a washout period for ACE-I of 36 hours. A starting dose of 49/51 mg is recommended for most patients, with a reduced starting dose of 24/26 mg twice daily to be considered for patients with systolic blood pressure <110 mmHg or GFR 30–60 ml/min/1.73m<sup>2</sup>. Blood pressure, renal function and serum potassium should be checked within the 2 weeks following initiation.<sup>4</sup>

### Pharmacological management of HF with mildly reduced EF

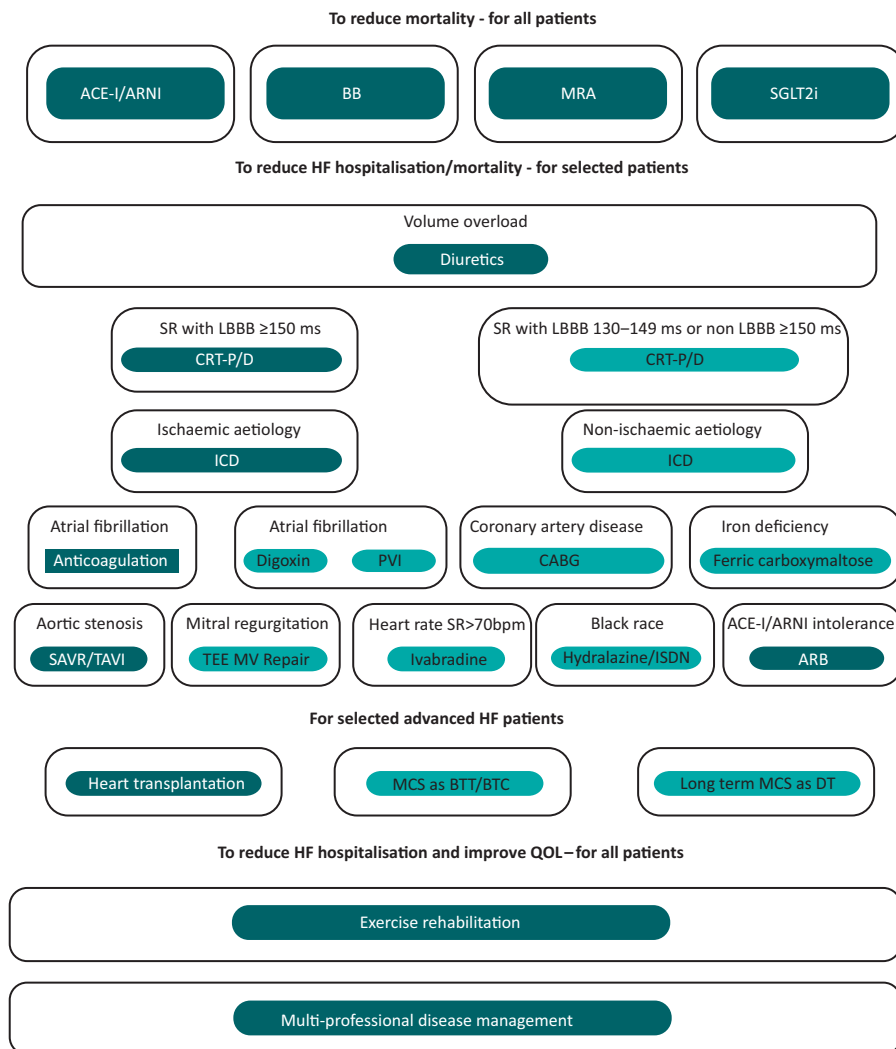
Guideline-directed pharmacological treatment of HFmrEF is similar to HFrEF but carries a weaker class IIB recommendation, meaning it ‘may be considered’, for RAASi/beta blockers/MRA, as evidence is derived solely from the sub-group analyses of non HFmrEF dedicated trials.<sup>4</sup>

### Pharmacological management of HF with preserved EF

Based on the DELIVER trial, NICE have recently approved the use of dapagliflozin for patients with HFpEF and HFmrEF.<sup>16,17</sup> The DELIVER (dapagliflozin) and the EMPEROR-Preserved (empagliflozin) trials in HFpEF and HFmrEF both demonstrated a reduction in the combined primary endpoint of cardiovascular death, worsening HF and HF hospitalisation.<sup>16,18</sup> All prior randomised pharmacological trials in HFpEF/HFmrEF had been negative. SGLT2 inhibitors are therefore the first drug class to demonstrate benefit across the spectrum of ejection fraction.

### The role of implantable cardiac devices

Device therapy is also indicated for many HFrEF patients. ESC guidelines recommend ICD implantation for symptomatic HF patients expected to live more than 1 year who, despite receiving 3 months of optimised GDMT, have a persisting LVEF of  $\leq 35\%$  for ischaemic (class I indication, ie is recommended)



**Fig 2. Summary of the management of HFrEF from the 2021 ESC HF guidelines.**<sup>4</sup> Dark teal indicates class of recommendation I ('indicated or recommended') and light teal indicates class of recommendation IIa ('should be considered'). ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; b.p.m. = beats per minute; BTC = bridge to candidacy; BTT = bridge to transplantation; CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; DT = destination therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = left bundle branch block; MCS = mechanical circulatory support; MRA = mineralocorticoid receptor antagonist; MV = mitral valve; PVI = pulmonary vein isolation; QOL = quality of life; SAVR = surgical aortic valve replacement; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SR = sinus rhythm; TAVI = transcatheter aortic valve replacement; TEE = transcatheter edge to edge.

and non-ischaemic aetiologies (class IIa indication, ie should be considered). For patients with HF and prolonged QRS duration, cardiac resynchronisation therapy (CRT) is indicated to improve morbidity and mortality.<sup>4</sup> (See Fig 2).

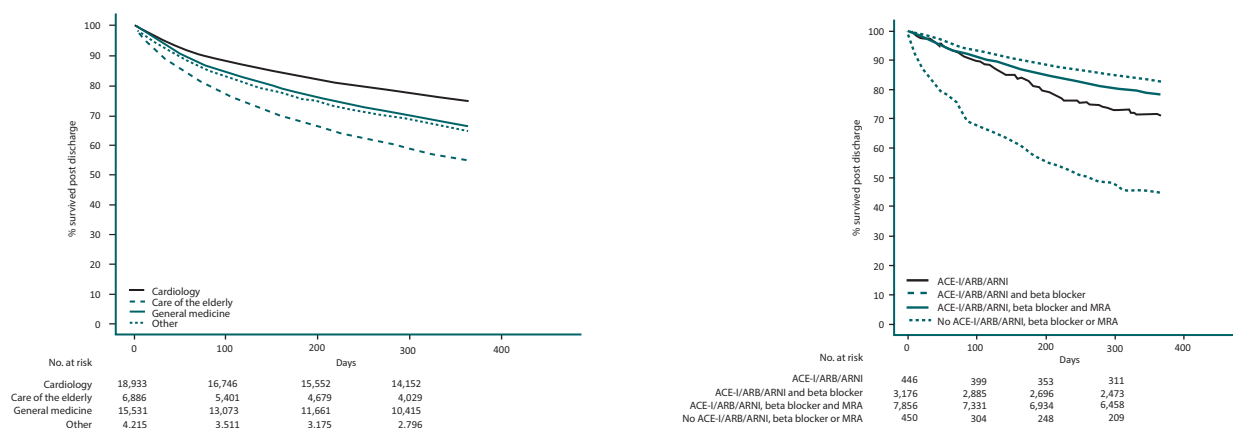
### Valvulopathy and HF

The emergence of percutaneous valve treatments including transcatheter aortic valve implantation (TAVI) has allowed many patients unfit for surgical aortic valve replacement (SAVR) to undergo aortic valve intervention for severe AS.<sup>4</sup>

Additionally, mitral regurgitation (MR) secondary to LV dilatation is common in HF. Percutaneous edge-to-edge mitral valve repair for MR may be considered for selected patients.<sup>4</sup>

### Revascularisation for chronic HF

Coronary revascularisation as a treatment for patients presenting with heart failure is increasingly controversial. Although the original STITCH trial was negative, in 2016 a 10-year follow up study to the STITCH trial was reported. Given this was an unplanned analysis, caution against overinterpretation of its results must be advised. Nonetheless, the follow-up study reported that patients with ischaemic HFrEF and surgically amenable coronary artery disease randomised to coronary artery bypass grafting (CABG) experienced lower rates of cardiovascular mortality than those receiving medical therapy alone.<sup>19</sup> However, this is not the case for revascularisation via percutaneous coronary intervention (PCI). The recently published



**Fig 3.** Data from National Heart Failure Audit (NICOR) 2021/2022.<sup>22</sup> Left panel: Kaplan Meier plot of all-cause mortality following discharge from hospital according to place of care during the admission. Right panel: Mortality following discharge associated with prescribing of HFpEF pharmacotherapy.

REVIVED-BCIS2 trial showed that in patients with extensive coronary disease plus 'viable' but mal-perfused myocardium, successful revascularisation with PCI did not reduce mortality or HF hospitalisation compared to medical therapy alone.<sup>20</sup>

## Prevention of HF

Smoking cessation, alcohol reduction, and management of obesity and sedentary lifestyles remain the focus of primary prevention for HF. SGLT2 inhibition has been shown to reduce incident heart failure in diabetes and is now recommended with metformin as the first line treatment for patients with type II diabetes and established or at risk of cardiovascular disease.<sup>16,21</sup> Patients with hypertension, obesity, chronic kidney disease and diabetes are at increased risk for development of heart failure. Lifestyle modification and weight loss plus optimal blood pressure control with RAASi are needed to reduce incident HF.

## Acute HF

Acute HF (AHF) carries a mortality risk of around 9% during admission and a post-discharge mortality of a further 33% over the next year.<sup>2</sup> AHF is usually triggered by an additional event such as fast atrial fibrillation, acute coronary syndrome, sepsis or recent cessation of HF pharmacotherapy. Successful management therefore requires investigation and treatment of both the precipitant and AHF simultaneously.

Recent progress in reducing the morbidity and mortality of AHF has related to optimisation of care pathways rather than discovery of new treatments. Survival is improved by early HF specialist input, triage to a cardiology ward, and discharge on optimised HF pharmacotherapy (Fig 3).<sup>3</sup>

The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) recommends NT-pro-BNP testing on the initial blood tests for all patients with suspected new heart failure. An NT-proBNP <300 pg/mL reliably excludes AHF and age-stratified rule-in cut-offs indicate acute HF is likely: >1800 pg/mL if aged >75 years, >900 pg/mL if aged between 55 and 75 years and >450 pg/mL if aged <55 years.<sup>4,24,25</sup> All patients admitted with AHF should be reviewed by a specialist HF service within 24 hours and should have echocardiography performed within 48 hours.<sup>26</sup>

ESC guidelines recommend that patients presenting acute pulmonary oedema or cardiogenic shock should be transferred to an intensive or coronary care unit within two hours to provide organ support and treat acute, reversible aetiologies such as: coronary syndromes, hypertensive emergencies, arrhythmias, mechanical obstruction, pulmonary embolism, infection, and tamponade (mnemonic: CHAMPIT).<sup>4</sup>

Admission with AHF provides a crucial opportunity to optimise HF therapy. Routine withdrawal of existing HF GDMT is not recommended in AHF, as this is associated with worsened outcomes. AHF patients should be discharged only once euvoelaemic, as residual oedema at discharge is associated with increased HF mortality and readmissions.<sup>27</sup> If there are no contraindications, patients with HFpEF should be discharged on 'four pillars' of HF pharmacotherapy and a stable dose of oral diuretic. Finally, IV iron is now a class IIa indicated treatment (meaning it should be considered) for iron deficient hospitalised HF patients with an LVEF <50%. The AFFIRM trial demonstrated that for iron deficient HF patients, intravenous iron reduced the composite secondary endpoint of HF hospitalisation or cardiovascular death.<sup>28</sup>

## Conclusion

Recent key developments in the management of chronic HF include: the EF independent effects of SGLT2 inhibition and evidence for HF incidence prevention in patients with type 2 diabetes and CKD; growing evidence of safety for ARNI initiation in acutely decompensated and ACE inhibitor naïve patients; and recently reported data from the REVIVED-BCIS2 trial which fundamentally questions the role that percutaneous revascularisation plays in the management of ischaemic heart failure. For all patients admitted with acute HF, ensure optimisation of fluid status and personalised pharmacotherapy and an ongoing HF management plan prior to discharge.

Modern HF treatment is increasingly effective; however, the prevalence of HF continues to rise worldwide. In addition, as HF treatments become more complex, the necessity for provision of specialist care increases too. Concerningly, in the UK, numbers of specialist HF doctors and allied health care professionals are already too low to meet existing clinical demand.<sup>29</sup> To effectively

address the global HF epidemic, more focus must be placed on primary prevention and risk factor modification. ■

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