Consensus statement on the current pharmacological prevention and management of heart failure

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The current pharmacological management of heart failure has been significantly improved by the use of angiotensin receptor neprilysin inhibitors, mineralocorticoid receptor antagonists, beta blockers, and diuretics to prevent heart failure and reduce mortality. Newer therapies, such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, cardiac myosin activator (omecamtiv mecarbil), and cardiac myosin activator (vericiguat), have been shown to improve outcomes in patients with heart failure.

Prevention of heart failure

The 2018 NHFA/CSANZ heart failure guidelines gave strong recommendations for blood pressure lowering and lipid lowering to prevent heart failure. Strong recommendations were also given for angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and mineralocorticoid receptor antagonists to prevent heart failure and reduce mortality. ACE inhibitors in patients with left ventricular systolic dysfunction and sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes mellitus associated with cardiovascular disease are recommended.

Prevention of heart failure with reduced LVEF (HFrEF)

Two trials evaluated a selective non-steroidal mineralocorticoid receptor antagonist (MRA), finerenone, in patients with type 2 diabetes mellitus with albuminuric chronic kidney disease (eGFR > 25 mL/minute/1.73 m²). The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial achieved its primary composite renal endpoint and secondary composite cardiovascular endpoint, the latter including a trend to decreased heart failure hospitalisation. The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial demonstrated a reduction in its primary composite cardiovascular endpoint, driven almost exclusively by decreased heart failure hospitalisation, including decreased new-onset heart failure.

Heart failure with reduced LVEF (HFrEF)

The 2018 NHFA/CSANZ heart failure guidelines strongly recommend an ACE inhibitor (or angiotensin receptor blocker [ARB]) if ACE inhibitors are contraindicated or not tolerated, beta blocker and MRA in all patients with HFrEF to decrease mortality and hospitalisation, and an angiotensin receptor neprilysin inhibitor (ARNI), sinus node inhibitor (ivabradine), diuretic and intravenous iron in selected patients. In this section, we will review new evidence regarding the use of an ARNI (sacubitril–valsartan), intravenous iron (ferric carboxymaltose), SGLT2 inhibitors (dapagliflozin, empagliflozin), and guanylate cyclase stimulator.
Patients with ambulatory heart failure showed sacubitril–valsartan was superior to enalapril for the primary efficacy endpoint of N-terminal pro-brain natriuretic peptide (NT-proBNP) reduction. The study
New recommendations to treat heart failure with reduced ejection fraction (LVEF ≤ 40%)

- Either an ARNI (sacubitril–valsartan) or ACE inhibitor (ARNI preferred) is recommended in patients with HFrEF (including newly diagnosed) to decrease mortality and decrease hospitalisation for heart failure (strong recommendation for; high quality of evidence).
- An ARNI (sacubitril–valsartan) is recommended as a replacement for an ACE inhibitor (with at least a 36-hour washout window) or ARB in patients with HFrEF despite receiving an ACE inhibitor (or ARB) and a beta blocker to decrease mortality and decrease hospitalisation for heart failure (strong recommendation for; high quality of evidence).
- An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFrEF to decrease mortality and decrease hospitalisation for heart failure (strong recommendation for; high quality of evidence).
- A soluble guanylate cyclase stimulator (vericiguat) may be considered in patients with persistent HFrEF and an LVEF ≤ 35% despite receiving maximally tolerated or target doses of a renin angiotensin system inhibitor, beta blocker and MRA to decrease cardiovascular death or hospitalisation for heart failure (weak recommendation for; moderate quality of evidence).
- A selective cardiac myosin activator (omecamtiv mecarbil) may be considered in patients with persistent HFrEF and an LVEF ≤ 35% despite receiving maximally tolerated or target doses of a renin angiotensin system inhibitor, beta blocker and MRA to decrease cardiovascular death or hospitalisation for heart failure (weak recommendation for; moderate quality of evidence).
- In patients with HFrEF associated with persistent symptoms despite optimised therapy, if the patient is iron deficient (ie, ferritin < 100 μg/L, or ferritin 100–299 μg/L with transferrin saturation < 20%), intravenous ferric carboxymaltose should be considered to improve symptoms and quality of life and decrease hospitalisation for heart failure (strong recommendation for; moderate quality of evidence).

Intravenous iron

The 2018 NHFA/CSANZ heart failure guidelines recommended that intravenous iron should be considered in patients with HFrEF associated with iron deficiency and persistent symptoms despite optimised therapy to improve symptoms and quality of life. Intravenous ferric carboxymaltose was recently evaluated in a placebo-controlled, randomised trial in patients hospitalised with acute heart failure (HFrEF or HfmrEF) with iron deficiency (ferritin < 100 μg/L, or ferritin 100–299 μg/L with transferrin saturation below 20%). While the study did not show a statistically significant difference between groups for the primary endpoint, there was a trend in favour of intravenous ferric carboxymaltose with a 21% relative risk reduction in the composite endpoint of cardiovascular death and total heart failure hospitalisations, driven by a nominally significant 26% relative risk reduction in total heart failure hospitalisations. Trial recruitment was affected by the COVID-19 pandemic, with the study showing that intravenous ferric carboxymaltose reduced the incidence of the primary endpoint in a prespecified, pre-COVID-19 sensitivity analysis. This study demonstrated that intravenous ferric carboxymaltose can be safely administered in patients hospitalised with acute heart failure and appears to decrease recurrent heart failure hospitalisation (Box 3). The effect of intravenous iron on cardiovascular mortality is being evaluated in ongoing clinical trials (NCT03037931, NCT03036462 and NCT02642562).

Guanylate cyclase stimulator

The oral soluble guanylate cyclase stimulator vericiguat was shown in a placebo-controlled, randomised trial to improve clinical outcomes in patients with HFrEF with evidence of worsening heart failure. The overall treatment effect was modest, with a 10% relative risk reduction in the primary endpoint, cardiovascular death or first hospitalisation for heart failure. While the study aimed to enrol patients with more severe heart failure, patients with an NT-proBNP level in the highest quartile appeared not to benefit. A subsequent analysis reported that the benefit of vericiguat extended to NT-proBNP levels up to 8000 pg/mL. This suggests that selected patients with progressive heart failure despite optimal medical therapy may benefit from the addition of vericiguat; however, patients with very advanced heart failure are less likely to benefit (Box 3).

Cardiac myosin activator

The selective cardiac myosin activator omecamtiv mecarbil was shown in a placebo-controlled, randomised trial to decrease the composite endpoint of cardiovascular death and heart failure hospitalisation in patients with HFrEF. The overall treatment effect was modest, with an 8% relative risk reduction in the primary endpoint. Prespecified subgroup analyses identified that patients with an LVEF above the median value of 28% and patients in atrial fibrillation or flutter may be less likely to benefit. A recent analysis confirmed that the LVEF was the strongest modifier of treatment effect among the prespecified subgroups. While this should be interpreted with caution, these interactions are biologically plausible given one might expect a cardiac myosin activator to have greater benefit in patients with a more severely reduced LVEF who remain in sinus rhythm. Furthermore, a post hoc analysis reported greater clinical benefit in patients with severe heart failure with an LVEF ≤ 30% and heart failure hospitalisation within 6 months. This suggests that selected patients with persistent heart failure and a severely reduced LVEF despite optimal medical therapy may benefit from the addition of omecamtiv mecarbil (Box 3).
Heart failure with preserved LVEF (HFrpEF)

The 2018 NHFA/CSANZ heart failure guidelines did not give specific treatment recommendations for patients with HFrpEF, given that none of the major HFrpEF randomised controlled trials had demonstrated a significant benefit of trialled interventions for the primary study endpoints.5

Angiotensin receptor neprilysin inhibitor

The PARAGON-HF study was done in patients with HFrpEF, and did not show a significant difference between sacubitril–valsartan and valsartan alone for the primary endpoint, with the addition of sacubitril leading to a 13% relative risk reduction in total heart failure hospitalisations and cardiovascular mortality (P = 0.06). The trend towards a benefit of sacubitril–valsartan over its active albeit unproven comparator, valsartan, was driven by reduced heart failure hospitalisation.35 Based on current evidence, despite the impression of a positive impact on heart failure hospitalisation from the addition of sacubitril to valsartan, no recommendation can be given to support its use in HFrpEF.

Sodium–glucose cotransporter 2 inhibitor

The EMPEROR-Preserved study, which enrolled patients with HFrpEF, demonstrated that empagliflozin led to a significant reduction in the primary endpoint of cardiovascular death or heart failure hospitalisation, mainly driven by a reduction in hospitalisation for heart failure.37 It is therefore reasonable to extend the HFrEF recommendation for SGLT2 inhibitors to patients with HFrpEF (Box 5).

Intravenous iron

The AFFIRM study, which evaluated intravenous ferric carboxymaltose in acute heart failure included patients with HFrpEF.35 While the trial was not powered for this subgroup, there was no significant heterogeneity according to LVEF. It is therefore reasonable to consider intravenous iron in such patients (Box 5).
5 New recommendations to treat heart failure with mildly reduced ejection fraction (LVEF 41–49%)

- Either an ACE inhibitor, ARNI (sacubitril–valsartan) or ARB may be considered in patients with HFrEF to decrease cardiovascular mortality or hospitalisation for heart failure (weak recommendation for; low quality of evidence).
- An SGLT2 inhibitor (empagliflozin) should be considered in patients with HFrEF to decrease cardiovascular mortality or hospitalisation for heart failure (strong recommendation for; moderate quality of evidence).
- In patients with HFrEF associated with persistent symptoms despite optimised therapy, if the patient is iron deficient (ie, ferritin < 100 mg/L, or ferritin 100–299 mg/L with transferrin saturation < 20%), intravenous iron (ferric carboxymaltose) may be considered to improve symptoms and quality of life and decrease hospitalisation for heart failure (weak recommendation for; low quality of evidence).

6 New recommendation to treat heart failure with preserved ejection fraction (LVEF ≥ 50%)

- An SGLT2 inhibitor (empagliflozin) should be considered in patients with HFpEF to decrease cardiovascular mortality or hospitalisation for heart failure (strong recommendation for; moderate quality of evidence).

HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; SGLT2 = sodium–glucose cotransporter 2.

Conclusions

Heart failure prevention remains a major health priority, with recent studies reporting that SGLT2 inhibitors and MRAs can prevent or delay the development of heart failure in patients with diabetic kidney disease. In all patients with established HFpEF, there is now strong evidence to support combining either an ARNI or ACE inhibitor with a beta blocker, MRA and SGLT2 inhibitor. Post hoc analyses support a similar approach in patients with HFrEF. Furthermore, the benefits of SGLT2 inhibitors extend to patients with HFpEF, with this being the first treatment to meet its primary endpoint in an HFrEF randomised controlled trial powered for major clinical outcomes. Additional therapies that may be considered in selected patients with HFpEF include vericiguat, omecamtiv mecarbil, and intravenous iron. Evidence gaps remain, including the need for additional therapies in patients with HFpEF, persistent HFrEF despite optimised therapy, and advanced heart failure.

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ook.html (viewed Apr 2022).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HFrEF = heart failure with mildly reduced ejection fraction; LVEF = left ventricular ejection fraction; SGLT2 = sodium–glucose cotransporter 2.


34 Okumura N, Jhund PS, Gong J, et al. Effects of sacubitril/valsartan in the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) according to background therapy. Circ Heart Fail 2016; 9: e003212.


