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The pharmacological prevention and management of heart failure: A consensus update

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Abbreviations used in this review:

ACE = angiotensin-converting enzyme
ARB = angiotensin receptor blocker
ARNI = angiotensin receptor neprilysin inhibitor
CKD = chronic kidney disease
CRT = cardiac resynchronisation therapy
CVD = cardiovascular disease
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
HF = heart failure
HFmrEF = heart failure with mildly reduced ejection fraction
HFpEF = heart failure with preserved ejection fraction
HFrEF = heart failure with reduced ejection fraction
LVEF = left ventricular ejection fraction
MRA = mineralocorticoid receptor antagonist
NYHA = New York Heart Association
QoL = quality of life
RAS = renin angiotensin system
SGLT2 = sodium-glucose cotransporter 2
SR = sinus rhythm
T2D = type 2 diabetes

This publication is an educational resource summarising changes in recommendations for the management of stable heart failure, as outlined in a recent Australian Consensus Statement. This includes treatments to prevent or delay the development of heart failure in patients with diabetic kidney disease, the wider and earlier use of an angiotensin receptor neprilysin inhibitor (ARNI) and SGLT2 inhibitor in those with established heart failure with reduced ejection fraction, and additional therapies for those with heart failure with mildly reduced or preserved ejection fractions.

Background

Heart failure (HF) is a complex syndrome causing reduced cardiac output and impaired delivery of blood to organs and metabolising tissues.[1] HF is the result of myocardial dysfunction that may be due to coronary artery disease, high blood pressure, heart defects, damage to cardiac muscle or arrhythmias.

The prevalence and incidence of HF is high. Almost 1 in 3 people aged 55 years in developed countries are predicted to develop HF during their lifetime.[2,3] There is limited data on the prevalence of HF in Australia, however, it has been estimated that 61,000 people aged ≥45 years are diagnosed each year with a conservative estimate of 480,000 Australians living with the condition.[4]

The current prognosis for people with HF is poor, regardless of their symptoms.[5] The mortality rate is 50% within 5 years of a diagnosis of HFrEF.[6] Indigenous Australians have higher HF morbidity and worse outcomes with a respective standardised prevalence and mortality ratio 1.7 and >2 times non-indigenous people.[7]

Hospitalisation due to HF is associated with markedly worse outcomes and a single admission due to HF increases the mortality risk by six-fold, compared to patients with HFrEF who have not been hospitalised.[8] It is estimated that HF in Australia results in over 1 million days in hospital per year at a cost of $2.7 billion.[4] Early detection and treatment of HF is critical as it is associated with fewer hospitalisations and improved outcomes.[9]

Definition and classification updates

A universal definition of HF was endorsed by the Cardiac Society of Australia and New Zealand in 2021.[10] This defined HF as 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.[10]

The new definition resulted in minor alterations in HF nomenclature such that HF with a LVEF ≤40% is referred to as HFrEF; HF with a LVEF of 41–49% is referred to as HFmrEF; and HF with a LVEF ≥50% is referred to as HFpEF.[11]

Preventing heart failure

Interventions to lower blood pressure and lipid levels remain crucial HF prevention strategies.[2,11–13] The use of ACE inhibitors and beta-blockers in patients with LV systolic dysfunction remains strongly recommended, as does the use of ACE inhibitors and SGLT2 inhibitors in patients with T2D and CVD.[2]

Practice point:[11]

- SGLT2 inhibitors are now strongly recommended to decrease the risk of developing HF in patients with T2D who are at high CV risk due to atherosclerotic CVD, multiple CV risk factors or macroalbuminuric CKD

This recommendation is based on multiple RCTs of SGLT2 inhibitors in patients with T2D with multiple CV risk factors or macroalbuminuric CKD (eGFR >30 mL/min/1.73m^2).[14–17]

Practice point:[11]

- An MRA (finerenone) may be considered to reduce the risk of HF in patients with T2D and albuminuric CKD who are taking a RAS inhibitor

This recommendation is based on two clinical trials of finerenone in patients with T2D and albuminuric CKD.[18,19] The first trial reported treatment with finerenone reduced the risk of CV events (composite secondary outcome), including a trend to decreased HF hospitalisation.[18] The second trial also reported a lower risk of CV events, primarily driven by a reduced incidence of HF hospitalisation, including decreased new-onset HF.[19,20]

Expert comment

Heart failure is common, causes significant impairment of quality of life, is expensive, leads to high risk of hospitalisation and has a high mortality. For these reasons, prevention of HF is of paramount importance. These new recommendations to reduce the risk of developing HF: with SGLT2 inhibitors in patients with T2D who are at high CV risk due to atherosclerotic CVD, multiple CV risk factors or macroalbuminuric CKD; and a MRA in patients with T2D and albuminuric CKD who are taking a RAS inhibitor are a call to action.

Patients with HF visit their GP on average 14 times a year, ranging from a mean of 11.7 times per year if no co-morbidities, to 27.2 per year, if >5 comorbidities.[21] GPs are the first point of contact and are ideally placed to identify and co-ordinate care for chronic diseases, like HF. Unfortunately, the diagnosis of HF in general practice needs to be improved with a recent study showing that in only 15% of patients with HF was it documented in the diagnosis section of their records and only 3.2% had their LVEF documented.[22] Keeping HF in mind as a possible cause of dyspnoea, fatigue and impairment of ability to perform usual physical activities will increase the diagnoses and prompt referral to a cardiologist for further investigation and management will improve care.

Treating HFrEF

Recent updates to international guidelines have resulted in changes to HFrEF management recommendations in Australia. Previously, a step-wise approach to the introduction of medicines was recommended following the initiation of an ACE inhibitor, beta-blocker and MRA in patients with HFrEF.[2] The problem with this approach is that it may delay the initiation of effective treatments.[11] Furthermore, the beneficial effects of ARNIs and SGLT2 inhibitors are now known to be detectable early in treatment and the initiation of these medicines is now recommended simultaneously with previously established treatments.

The overarching principle of the updated HFrEF management guidance is that the four pillars of therapy, i.e. ARNI/ACE inhibitor, beta-blocker, MRA and SGLT2 inhibitor, should be initiated as soon as clinically possible (**Figure 1**).[11] In patients with congested HFrEF, the beta-blocker should be initiated once they are euvolaemic. The four first-line therapies should be up-titrated to the maximum tolerated dose, generally beginning with the beta-blocker, unless the patient is congested or has a heart rate <50 bpm.

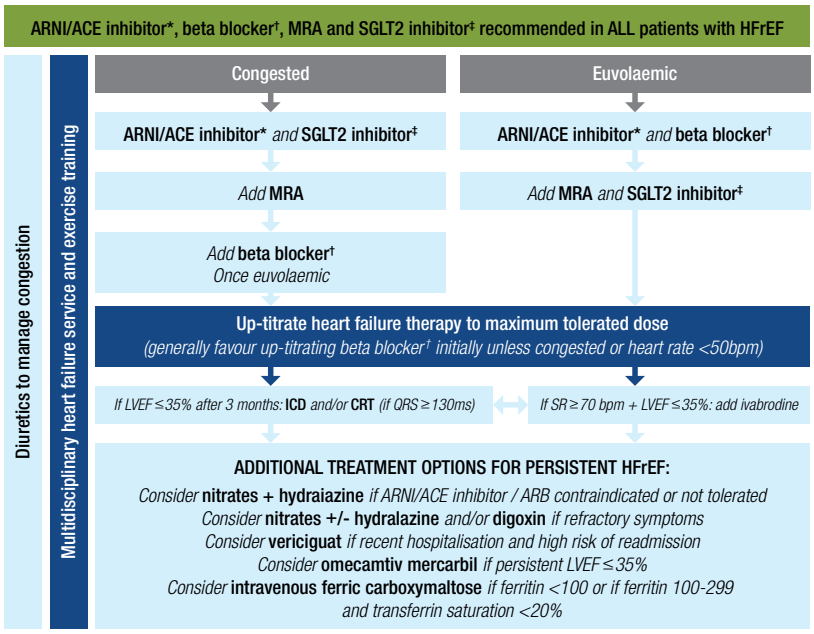


Figure 1. Management algorithm for patients with heart failure with reduced ejection fraction based on the presence or absence of clinical congestion. Adapted from Sindone *et al* (2022)[11]

† Carvedilol, bisoprolol, metoprolol succinate or nebivolol recommended; ‡ Dapagliflozin or empagliflozin recommended; * ARNI preferred. ACE inhibitor can be considered as an alternative if problematic hypotension, and consider switching to ARNI later.

Early initiation of an ARNI

Practice points:[11]

- Either an ARNI (sacubitril/valsartan) or an ACE inhibitor (ARNI preferred) is strongly recommended in patients with HFrEF (including newly diagnosed) to decrease both mortality and HF hospitalisation
- An ARNI (sacubitril/valsartan) is strongly recommended as a replacement for an ACE inhibitor (with at least a 36-hour washout) or ARB to decrease both mortality and HF hospitalisation

N.B. Sacubitril/valsartan should be considered a first-line treatment for HFrEF only if it does not compromise the initiation of other first-line therapies. An ACE inhibitor may be started and switched to sacubitril/valsartan following the initiation and up-titration of other medicines.

The PARADIGM-HF trial had previously shown an additional benefit to HFrEF patients when neprilysin inhibition was added to a RAS inhibitor.[23,24] *Post hoc* analysis of the PARADIGM-HF trial showed readmission rates for any cause at 30 days were 21.0% in patients receiving enalapril and 17.8% in those receiving sacubitril/valsartan (**Figure 2**; OR 0.74; 95% CI 0.56-0.97; p=0.031).[25] Readmission rates for HF at 30 days were also reduced in patients receiving sacubitril/valsartan (9.7%) versus enalapril (13.4%; OR 0.62; CI 0.45-0.87; p=0.006). Reductions in both all-cause and HF readmissions persisted at 60 days.

The safety and efficacy of sacubitril/valsartan was further demonstrated in the setting of acute decompensated HFrEF in the PIONEER-HF and TRANSITION studies.[26,27]

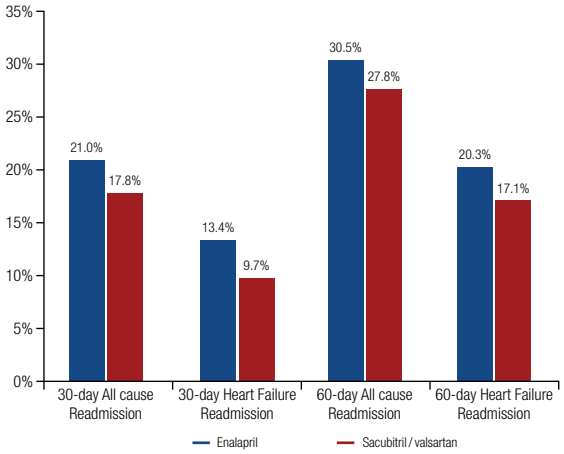


Figure 2. Readmission rates following investigator-reported hospitalisations in PARADIGM-HF for patients treated with enalapril or sacubitril/valsartan. Adapted from Desai *et al* (2016).[25]

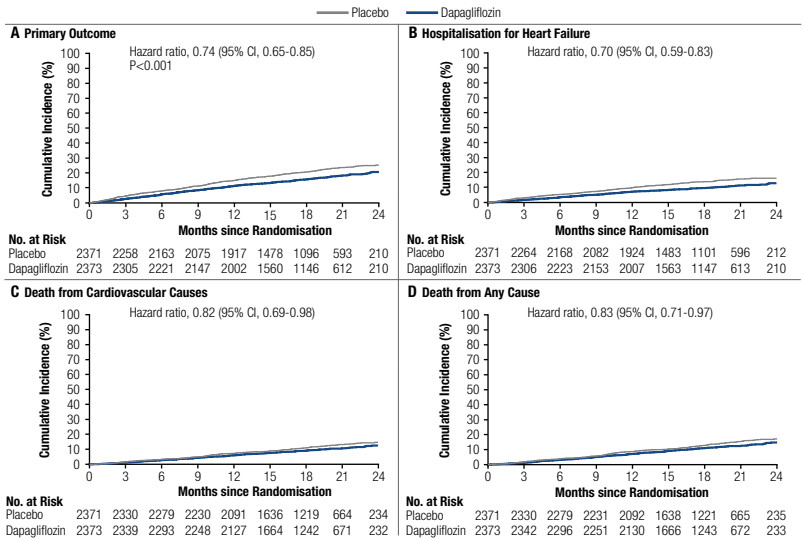
Early initiation of an SGLT2 inhibitor

Practice point:[11]

- An SGLT2 inhibitor (dapagliflozin or empagliflozin) is strongly recommended in patients with HFrEF to decrease both mortality and HF hospitalisations

The benefits and safety of SGLT2 inhibitors in patients with HFrEF have been demonstrated in multiple RCTs and meta-analyses.[28–32] Two seminal studies in this evidence were the DAPA-HF and EMPEROR-Reduced trials.[28,29]

DAPA-HF was a phase 3, placebo-controlled trial that randomly allocated 4,744 patients with NYHA class II, III, or IV HF and an EF ≤40% to dapagliflozin or placebo, in addition to standard care.[28] The primary outcome was a composite of worsening HF or CV death. Over a median of 18.2 months, the risk of worsening HF or CV death was lower in patients receiving dapagliflozin compared to placebo, regardless of the presence or absence of diabetes. This significant reduction in the composite primary endpoint was due to reductions in HF hospitalisation and CV mortality (**Figure 3**).



The primary outcome was a composite of death from CV causes, hospitalisation for HF, or an urgent visit resulting in intravenous therapy for HF

Figure 3. Cumulative incidence and hazard ratios for the primary outcome (A), hospitalisation for HF (B), CV death (C), and all-death (D) for patients receiving dapagliflozin or placebo in the DAPA-HF trial. Adapted from McMurray *et al* (2019).[28]

EMPEROR-Reduced was also a double-blind, placebo-controlled trial in which 3,370 patients with class II, III, or IV HF and an EF ≤40% received empagliflozin or placebo, in addition to standard care.[29] The primary outcome was a composite of CV death or hospitalisation for worsening HF. The authors reported a significant reduction in the composite primary endpoint in patients receiving empagliflozin compared to placebo, and again this occurred in the presence or absence of diabetes.[29] The benefit of empagliflozin was driven by a significant reduction in HF hospitalisation and a non-significant reduction in CV mortality. A meta-analysis of DAPA-HF and EMPEROR-Reduced reported that SGLT2 inhibitors were associated with significant relative risk reductions in all-cause mortality (13%; p=0·018), CV mortality (14%; p=0·027), first HF hospitalisation (31%; p<0.001) and first kidney composite event (38%; p=0.013).[30]

SGLT2 inhibitors in patients with HFrEF have been shown to result in statistically significant benefits within 28 days of initiating treatment.[33,34]

Additional treatments for persistent HFrEF

For patients with persistent HRrEF despite the use of first-line treatments at maximum tolerated doses, hydralazine plus nitrates continue to be a treatment option to decrease mortality if an ACE inhibitor and ARB are contraindicated or not tolerated.[2,11] Nitrates with or without hydralazine and/or digoxin may be considered in HFrEF patients with refractory symptoms.[11]

Guanylate cyclase stimulator

The guanylate cyclase stimulator vericiguat is now recommended for consideration in patients recently hospitalised with HFrEF who are at high risk of readmission.[11]

Practice point:[11]

- Vericiguat may be considered to decrease CV death or HF hospitalisation in patients with persistent and recent worsening HFrEF, despite maximal or target doses of a RAS inhibitor, beta-blocker and MRA

A phase 3 RCT of 5,050 patients with chronic HF with an EF <45% found that over a median of 10.8 months, the primary composite outcome of CV death or first HF hospitalisation occurred in 35.5% of the vericiguat arm and 38.5% of the placebo arm (HR 0.90; 95% CI 0.82-0.98; p=0.02).[35] The benefits of vericiguat have been shown to include patients with NT-proBNP levels ≤8,000 pg/ml.[36]

Cardiac myosin activator

The selective cardiac myosin activator omecamtiv mecarbil is now recommended for consideration in patients with HFrEF and a persistent LVEF ≤35%.[11]

Practice point:[11]

- Omecamtiv mecarbil may be considered to prevent CV death or HF hospitalisation in patients with persistent HFrEF and LVEF ≤35%, despite maximal or target doses of a RAS inhibitor, beta-blocker and MRA

Patients with severely reduced LVEF despite optimal therapy may gain the greatest benefit from omecamtiv mecarbil, while HFrEF patients in AF or flutter may be less likely to benefit.[11] A phase 3 RCT randomised 8,256 patients with chronic HF and an EF ≤35% to omecamtiv mecarbil or placebo, in additional to standard care.[37] Over a median of 21.8 months, the primary composite outcome of first HF event or CV death occurred in 37% of the omecamtiv mecarbil arm and 39.1% of the placebo arm (HR 0.92; 95% CI 0.86-0.99; p=0.03).[37] A prespecified subgroup analysis found that patients with an LVEF above the median of 28% were less likely to benefit, as were those in AF or flutter; these results are supported by additional analyses.[37–39]

Intravenous iron

Previously, IV iron was recommended for patients with HFrEF with iron deficiency and persistent symptoms despite optimised therapy.[2]

Practice point:[11]

- IV ferric carboxymaltose should be strongly considered to improve symptoms and QoL and decrease HF hospitalisation for HFrEF patients with persistent symptoms despite optimised therapy if they are iron deficient*

* Iron deficiency is considered to be ferritin <100 mg/L or ferritin 100-299 ug/L with a transferrin saturation <20%.[11]

The AFFIRM study randomly assigned 1,132 patients hospitalised with acute HF and iron deficiency and an LVEF <50% to IV ferric carboxymaltose or placebo for up to 24 weeks.[40] The primary composite outcome of first HF hospitalisation or CV death occurred in 32% of patients receiving IV iron and 38% in the placebo group (HR 0.80; 95% CI 0.66-0.98; p=0.03), although there was no significant difference in CV death between the groups.[40] Serious adverse events occurred in 45% of the IV iron group and 51% of the placebo group.

Expert comment

There have been a number of landmark, practice changing studies in the last four years which led to the need for the new Consensus Statement for the management of HF. These trials have shown a benefit of ARNIs over ACE inhibitors in HFrEF, including in newly diagnosed patients. Other trials have shown the incremental benefits of the addition of an SGLT2 inhibitor to standard therapy in HFrEF. Because of these findings, it is now recommended that all patients with HFrEF are initiated on the four pillars of therapy: ARNI (ACE inhibitor only if unable to tolerate an ARNI due to hypotension), beta-blocker, MRA and now SGLT2 inhibitor. The important point is that all four medications should be initiated as soon as possible because the benefits occur early.

The guidance in the treatment algorithm is, in congested patients, to initiate ARNI and SGLT2 inhibitors at diagnosis, quickly followed by MRA. Once the patient is euvolaemic, a beta-blocker should be added. In hospitalised patients, these should be initiated prior to discharge. In euvolaemic patients, an ARNI and beta-blocker should be initiated at diagnosis, quickly followed by MRA and SGLT2 inhibitor.

For patients who have had a recent decompensation requiring hospitalisation or intravenous therapy, vericiguat should be considered to reduce the risk of HF hospitalisation or CV death.

Other treatments which may be considered if a patient is still symptomatic or cannot tolerate the four pillars of HF therapy include: nitrates, hydralazine and omecamtiv mecarbil, which is a cardiac myosin stimulator which increases actin/myosin coupling (more hands on the rope). These are additional weapons in the war against a very difficult to control and potentially lethal enemy – heart failure.

Treating co-morbidities improves symptoms and may also reduce hospitalisations in patients with HF. Many studies have shown that intravenous iron infusions in patients with HFrEF and iron deficiency, almost all using ferric carboxymaltose, improve symptoms, reduce hospitalisations and lead to a trend towards a reduction in overall mortality. This is due to improvements in mitochondrial function, oxidative phosphorylation and muscle function but is independent of anaemia. This has been confirmed in a recent meta-analysis.[41]

Doctors in primary care should make sure that their patients with HFrEF, if appropriate, are receiving the four pillars of HF therapy and refer these patients to a cardiologist for review to uptitrate their treatment, if necessary.

Treating HF with mildly reduced LVEF

In patients with HFmrEF (LVEF 41-49%), consideration of an ACE inhibitor/ARB, beta-blocker and MRA continues to be recommended.[2,11] Subgroup and *post hoc* analysis now provide evidence for the consideration of additional therapies in patients with HFmrEF.

Practice point:[11]

- Either an ACE inhibitor, ARNI (sacubitril/valsartan) or ARB may be considered to decrease CV mortality or HF hospitalisation in patients with HFmrEF

A combined analysis of the PARADIGM-HF and PARAGON-HF trials found that patients with HFmrEF also gain a benefit from treatment with sacubitril/valsartan.[42]

Practice point:[11]

- An SGLT2 inhibitor (empagliflozin) should be strongly considered to decrease CV mortality or HF hospitalisation in patients with HFmrEF

The EMPEROR-Preserved trial (see below) included patients with HFmrEF and found a nominally statistically significant benefit associated with empagliflozin in patients with HFmrEF.[43]

Practice point:[11]

- IV ferric carboxymaltose may be considered to improve symptoms and QoL and decrease HF hospitalisation in patients with HFmrEF and persistent symptoms if they are iron deficient, despite optimised therapy

The AFFIRM study of IV iron in acute HF included patients with HFmrEF and no significant heterogeneity was reported according to LVEF.[11,40]

Treating HF with preserved LVEF

Previous guidelines did not provide specific recommendations for the treatment of patients with HFpEF, as none of the major RCTS had demonstrated a significant benefit in primary endpoints.[2,11] More recent evidence now supports recommending SGLT2 inhibitors in patients with HFpEF.[11]

Practice point:[11]

- An SGLT2 inhibitor (empagliflozin) should be strongly considered to decrease CV mortality or HF hospitalisation in patients with HFpEF

The EMPEROR-Preserved trial randomly assigned 5,988 patients with class II-IV HF and an EF >40% to empagliflozin or placebo, in addition to standard care.[43] Over a median of 26.2 months, the primary composite outcome of CV mortality or HF hospitalisation occurred in 13.8% of the empagliflozin group and 17.1% of the placebo group (HR 0.79; 95% CI 0.69-0.90; p<0.001).[43] The benefit of empagliflozin appeared to be consistent in patients with or without diabetes and was largely driven by a reduced risk of HF hospitalisation. This is the first treatment in a trial of patients with HFpEF powered for major clinical outcomes to meet its primary endpoint.[11]

Expert comment

HFmrEF patients appear to benefit from similar treatments to patients with HFrEF, but the degree of benefit and the evidence for this benefit is less robust. Hence, the strength of the recommendations for these therapies in HFmrEF is less strong. Nevertheless, these patients are still at risk of hospitalisation and deteriorating clinical status and treatment with ARNI and SGLT2 inhibitors should be considered in the management of these patients.

Until recently, no treatment had been shown to improve outcomes in patients with HFpEF. Two trials have now shown reductions in CV mortality and HF hospitalisation using the SGLT2 inhibitors empagliflozin and dapagliflozin, regardless of the presence of diabetes.[43,44] This data has the potential to revolutionise the management of HFpEF by treating these patients with SGLT2 inhibitors which could have a major impact on the health care economy, as HFpEF now accounts for almost half of all HF hospitalisations and the average length of stay is approximately seven days. Reducing this burden of hospitalisations will be a great advance in the management of this difficult to treat condition.

Doctors in primary care are perfectly placed to recognise patients who may potentially have HFpEF or HFmrEF and arrange initial investigations with biochemistry, ECG and chest X-ray and refer these patients to a cardiologist for further investigation and management. These patients now have treatments which can lead to meaningful benefits in their symptoms and prognosis.

Take-home messages

- To reduce the risk of developing HF, SGLT2 inhibitors are strongly recommended in patients with T2D who are at high CV risk due to atherosclerotic CVD, multiple CV risk factors or macroalbuminuric CKD
- In general, for patients with HFrEF an ARNI/ACE inhibitor, beta-blocker, MRA and SGLT2 inhibitor should be initiated as soon as clinically possible; if the patient is congested the beta-blocker should be started once euvolaemia is achieved.
- Dapagliflozin or empagliflozin are strongly recommended in all patients with HF, i.e. HFrEF, HFmrEF and HFpEF, to decrease both mortality and HF hospitalisations
- Sacubitril/valsartan (preferred) or an ACE inhibitor are strongly recommended in patients with HFrEF (including newly diagnosed) to decrease both mortality and HF hospitalisation
- Sacubitril/valsartan is strongly recommended as a replacement for an ACE inhibitor (with at least a 36-hour washout) or ARB to decrease both mortality and HF hospitalisation
- Up-titrate all first-line therapies to a maximum tolerated dose in patients with HFrEF before considering additional pharmacotherapies
- IV ferric carboxymaltose should be strongly considered for patients with HFrEF or HFmrEF who are iron deficient and have persistent symptoms despite optimised therapy

Expert's concluding remarks

A great deal has changed in the last few years in the management of patients with HF, which still has a very poor prognosis. All patients with HFrEF, if possible should be treated with the four pillars of ARNI/ACE inhibitor, beta-blocker, MRA and SGLT2 inhibitor. These treatments should be initiated early and then uptitrated, as tolerated. Identification of patients with HF in primary care is very important so that patients have the opportunity to benefit from these new advances in treatment.

There are additional treatments which can be given to patients with persistent symptoms and referral to a cardiologist for ongoing investigation and management will allow patients to receive optimal care to improve symptoms, reduce hospitalisation and improve survival.

Patients with HFmrEF and HFpEF, conditions which previously had little or no evidence of treatments which improved outcomes now may benefit from SGLT2 inhibitors. Other treatments have the potential to lead to further small improvements.

We now have more weapons in the war against HF and implementing Guideline Directed Medical Therapy will, hopefully, reduce the high rate of hospitalisation and death in patients with HF, improve their quality of life and have them living on with more effective therapy.

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