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Overview of Updated International Recommendations for Treatment of Chronic HF: Focus on the Role of ARNIs for HFrEF

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Abbreviations used in this issue:

ACC = American College of Cardiology
ACEI = angiotensin-converting enzyme inhibitor
AF = atrial fibrillation
AHA = American Heart Association
ARB = angiotensin II receptor blocker
ARNI = angiotensin receptor-neprilysin inhibitor
BNP = B-type natriuretic peptide
CCS = Canadian Cardiovascular Society
CHFS = Canadian Heart Failure Society
CSANZ = Cardiac Society of Australia and New Zealand
CaReMe UK = Cardio-Renal-Metabolic United Kingdom Partnership
ECS = European Society of Cardiology
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 (aldosterone) receptor antagonist
NHFA = National Heart Foundation of Australia
NT-proBNP = N-terminal pro–B-type natriuretic peptide
PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
PIONEER-HF = Comparison of Sacubitril/valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode
RAAS = renin-angiotensin-aldosterone (mineralocorticoid) system
RAASi = renin-angiotensin-aldosterone (mineralocorticoid) system inhibitor
RAS = renin-angiotensin system
RASI = renin-angiotensin system inhibitor
sGC = soluble guanylate cyclase
SGLT2 = sodium-glucose cotransporter-2
TGA = Therapeutic Goods Association

With the rapid emergence of new evidence and availability of additional medications, major international expert consensus recommendations on the management of chronic HF have been updated. This review provides a top-line summary of updated international recommendations relative to those of the existing Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 for the pharmacological treatment of chronic HFrEF, highlighting the positioning of ARNIs earlier in the treatment algorithm.

Definition of heart failure

HF is a complex clinical syndrome with typical symptoms and signs (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, and fatigue) that generally occur on exertion but can also occur at rest.[1,2] HF results from a cardiac structure or function abnormality that impairs left ventricular filling or ejection of blood, or both.

A recently proposed universal definition of HF is: 'a clinical syndrome with current or prior 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'.[3] Also proposed is a new and revised classification of HF according to LVEF, which includes HFrEF as HF with LVEF ≤40% and HFmrEF as HF with LVEF 41–49%. In the Australian 2018 guidelines, HFrEF is defined as the clinical symptoms with or without signs of HF and a measured LVEF of <50% and if LVEF is mildly reduced, i.e. HFmrEF as HF with LVEF 41–49%, additional criteria are required (e.g. signs of HF or objective signs of high filling pressure).[1]

Disease burden

HF affects an estimated 23 million people globally, of which approximately half have HFrEF.[2] HFrEF is associated with high levels of morbidity and mortality. Patients with HFrEF have markedly shorter life expectancies compared with the general population.[4,5] The 5-year survival rate is 25% following hospitalisation.[2]

Applying international epidemiological and clinical study data to Australian Bureau of Statistics (ABS) population figures for 2014, Chan et al. estimated the prevalence of HF to be 2.1% and its annual incidence 0.27%.[6] They estimated that 480,000 Australians were affected by HF with 61,000 new cases of HF occurring every year. More recently, a study of HF in the general Australian community over the period 2013–2018 found a prevalence of 1.8% for HF and incidence of 0.29% per year.[7] These data suggested that almost 420,000 people were living with HF in Australia in 2017 and that over 66,000 new cases of HF occurred that year.

In terms of healthcare resource use, there were approximately 181,200 hospitalisations in 2018–2019 where HF and cardiomyopathy were recorded as the main or additional diagnosis, representing 1.6% of all hospitalisations in Australia, according to self-reported data from the most recent ABS National Health Survey.[8] Based on ABS population data for 2014, Chan et al. estimated >150,000 hospitalisations and >1 million days in hospital per year due to HF.[6] The annual cost of managing HF in Australia in the community was approximately $900 million and nearly $2.7 billion factoring in the additional cost of in-patient care.

As the prevalence of HF increases with age,[9] the ageing Australian population is expected to further increase the burden of HF.[6,7]

Pharmacological targets

The modulation of a variety of pathophysiological targets with pharmacological therapy (**Table 1**) has been shown to relieve symptoms and improve clinical outcomes in patients with chronic HFrEF.[10,11] Pharmacologic therapy has the potential to extend survival by up to 6 years and event-free survival by up to 8 years.[12]

Table 1. **Pathophysiological targets in chronic HFrEF and the pharmacologic therapies directed at those targets.**[10,11]

Pathophysiological target	Pharmacological therapy
Renin-angiotensin-aldosterone (mineralocorticoid) system	ARNIs/ACEIs/ARBs, aldosterone (mineralocorticoid) receptor antagonists (MRAs)
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitors (ARNIs)
Sodium-glucose cotransporter-2	SGLT2 inhibitors†
Elevated heart rate	Beta-blockers, ivabradine
Relief of congestion	Diuretic agents
Cyclic guanosine monophosphate pathway	sGC stimulators¥
Myocardial contractility	Cardiac myosin activators¥

†Only dapagliflozin is TGA approved. ¥Unregistered products.

Beta-blockers and RAASis have become the principal pharmacological interventions used in the treatment of HF.[13] However, despite the established efficacy of these pharmacotherapies, morbidity and mortality remain high, which has driven the development of novel molecular targets.

Notable advances in pharmacotherapy for HFrEF have occurred in recent decades.[12] In particular, three drug classes have been shown to reduce morbidity and mortality in HFrEF beyond that of the already established RAASis and beta-blockers in patients with HFrEF.[12,14] Clinical trials have demonstrated superiority (lower risk of morbidity and death) of MRAs compared with placebo added to standard therapy.[15,16] In the PARADIGM-HF and PIONEER-HF trials, combining an ARB with a neprilysin inhibitor (ARNI), sacubitril/valsartan, was superior in improving clinical outcomes when directly compared with an ACEI.[17-19] The risk of worsening HF or death from cardiovascular causes was further lowered in those who received SGLT2 inhibitors† than in those who received placebo, when added to standard therapy (ACEI, ARB, or ARNI plus a beta-blocker, with or without an MRA).[20]

More recently, the sGC stimulator, vericiguat¥ in addition to guideline-based medical therapy, was shown to reduce hospitalisation for HF (versus placebo) in patients with high-risk HFrEF.[21] Not yet included in HF guidelines is omecamtiv mercarbil¥, a first-in-class cardiac myosin activator that increases cardiac contractility by specifically binding to the catalytic S1 domain of cardiac myosin.[11] Treatment with omecamtiv mecarbil¥, added to standard HF therapy, has been demonstrated to be associated with a lower incidence of a composite of a HF event or death from cardiovascular causes compared with placebo in patients with HF and a reduced ejection.[22]

Pharmacotherapy approaches

In general, unless specific medication contraindications or intolerances exist, an ARNI or ACEI, a beta-blocker and an MRA are foundational pharmacological therapy for HFrEF.[2,14,23] The addition of a SGLT2 inhibitor† to foundational therapies can further improve outcomes, irrespective of diabetes status. Diuretics are used for symptom relief in patients with fluid retention. Ivabradine and hydralazine/isosorbide dinitrate are used in select patients with HFrEF. Digoxin is used for patients with persistent symptoms in the setting of atrial fibrillation. The respective roles of the sGC stimulator, vericiguat¥, and cardiac myosin activator, omecamtiv mecarbil¥, in HFrEF therapy have yet to be fully defined.

Treatment recommendations

The current Australian treatment guidelines for HF were published in 2018.[1] The years since their publication have witnessed the accumulation of additional clinical experience and real-world evidence with ARNIs and arrival of SGLT2 inhibitors†. Clinical experience is also being accumulated with vericiguat¥. Differences and similarities among the Australian 2018 guidelines, 2021 update of the US ACC expert consensus decision pathway, 2021 CaReMe UK management algorithm, 2021 update of the Canadian guidelines, and the 2021 European guidelines for the key medications used in the treatment of chronic HFrEF are summarised in **Table 2**. Note that the individual consensus recommendations or guidelines should be consulted for full details of the recommendations and contraindications for each medication class, including the specific clinical settings in which they may be prescribed.

ARNI therapy

An ARNI is recommended as a first-line treatment in the 2021 update of the US ACC expert consensus decision pathway, 2021 CaReMe UK management algorithm, 2021 European guidelines, and 2021 update of the Canadian consensus recommendations,[10,23-25], whereas an ARNI is recommended as a second-line treatment in the Australian 2018 guidelines (**Table 2**).[1] The difference in recommendation is likely to be partially due to the latest US, UK, European, and Canadian recommendations or guidelines having available at the time of their compilation more recent new and emerging evidence for the pharmacologic treatment of HFrEF, including pivotal clinical trials demonstrating the efficacy of the ARNI sacubitril/valsartan.

† Dapagliflozin is the only SGLT2 inhibitor approved by the TGA for treatment of HF. ¥ Unregistered product.

US decision pathway: 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment

ARNI therapy is considered to be a well-established treatment for chronic HFrEF, with ARNIs being the preferred (if possible) renin-angiotensin inhibitor as first-line therapy in HFrEF (**Table 2**).[10]

The update states: 'ARNIs have been associated with improvement in diastolic function, left ventricular function, quality of life, and burden of ventricular arrhythmias'.

UK algorithm: CaReMe UK 2021 Heart Failure Management Algorithm

The CaReMe UK 2021 HF algorithm is a modified version of the chronic HF management algorithm from the NICE guideline (NG106) Chronic Heart Failure in Adults: Diagnosis and Management.

An ARNI is recommended as a first-line option for treatment of HFrEF (if LVEF <35%) [**Table 2**].[25]

The Cardio-Renal-Metabolic (CaReMe) UK Partnership is a collaboration of the British Cardiovascular Society, Renal Association, Association of British Clinical Diabetologists, Primary Care Cardiovascular Society, and Primary Care Diabetes Society.

Canadian guidelines: CCS/CHFS Heart Failure Guidelines Update 2021

Acknowledging that 'ARNI therapy is now a well-established treatment recommendation in patients with chronic HFrEF who have been previously exposed to either ACEIs or ARBs', an ARNI is recommended either as first-line therapy or switching from an ACEI or ARB (**Table 2**).[24]

More specifically:[24]

- An ARNI be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses to decrease cardiovascular death, HF hospitalisations, and symptoms.
- Patients admitted to hospital for acute decompensated HF with HFrEF should be switched to an ARNI, from an ACEI or ARB, when stabilised and before hospital discharge.
- Patients admitted to hospital with a new diagnosis of HFrEF should be treated with an ARNI as first-line therapy, as an alternative to either an ACEI or ARB.

The guidelines also note that because an ARNI might reduce diuretic requirements, diuretic dosing should be carefully evaluated when starting ARNI therapy.[24]

European guidelines: ESC Heart Failure Guidelines 2021

An ARNI is considered a cornerstone therapy for HFrEF (**Table 2**).[23] More specifically, the guidelines recommend: 'the use of ARNI as a replacement for ACEI in suitable patients who remain symptomatic on ACEI, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACEI'.

The guidelines also state that treatment with an ARNI may be considered in patients with HFmrEF, defined as the presence of symptoms and/or signs of HF and a LVEF 41–49%.[23]

Australian guidelines: 2018 National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines

An ARNI is included in the 'Medications Recommended in Selected Patients with HFrEF' and not yet part of the 'Medications Recommended in All Patients with HFrEF' sections of the guidelines.[1]

More specifically: 'An ARNI is recommended as a replacement for an ACEI (with at least a 36-hour washout window) or an ARB in patients with HFrEF despite receiving maximally tolerated or target doses of an ACEI (or ARB) and a beta-blocker (unless contraindicated), with or without an MRA, to decrease mortality and decrease hospitalisation' (**Table 2**).[1]

Table 2. Top-line differences and similarities among major guideline/expert consensus recommendations for key medications (unless contraindicated or not tolerated) in the treatment of chronic HFrEF (defined as LVEF ≤40%, unless otherwise specified).

	Guideline/Expert Consensus Recommendations*				
	Australia	UK	US	Canada	Europe
	NHFA and CSANZ 2018 guidelines[1]	CaReMe 2021 algorithm[25]	ACC 2021 algorithm update[10]	CCS/CHFS 2021 guidelines update[24]	ESC/HFA 2021 guidelines[23]
ACEIs	1st line	1st line	1st line	1st line	1st line
ARBs	1st line (if ACEI is contraindicated or not tolerated)	1st line (if intolerant of ACEI)	1st line	1st line	1st (if intolerant of ACEI or ARNI)
ARNI	2nd line	1st line (if LVEF <35%)	1st line (preferred agent)	1st line (or as switch from ACEI or ARB)	1st line
Beta-blockers	1st line	1st line	1st line	1st line	1st line
MRAs	1st line	1st line	2nd line	1st line	1st line
SGLT2 inhibitors†	Not specified for HFrEF	2nd line	2nd line	1st line	1st line
Diuretics	1st line (for congestive symptoms)	1st line (for congestive symptoms and fluid retention)	1st line (as needed for symptom relief)	1st line (to maintain euvoleamia)	1st line (for congestive symptoms)
Digoxin	2nd line	Not in algorithm	Indicated for HFrEF as a rate control agent for AF in those with low BP	2nd line for select populations	Should be considered in select populations
Hydralazine + isosorbide dinitrate	2nd line	Not in algorithm	1st line for African Americans	Possibly useful in select populations	Should be considered in select populations
Ivabradine	2nd line (if LVEF ≤35% and sinus rate 70 bpm)	Not in algorithm	2nd line for select populations	2nd line for select populations	Should be considered in select populations
sGC stimulators¥	Not in guidelines	Not in algorithm	Discussed but no specific recommendation	Consider in select populations	May be considered in select populations

*Consult the individual guidelines/algorithms for full details of the recommendations and contraindications for each medication class, including the specific clinical settings in which they may be prescribed. † Only dapagliflozin is TGA approved. ¥Unregistered products.

Expert's comments: Current guideline recommendations for HFrEF

The Australian HF guidelines from 2018 for HFrEF give strong recommendations, with a high level of evidence, for the use of ACEI or ARB (if ACEI intolerant), MRA, and beta-blocker. The algorithm stipulates two streams, one for congested patients where the ACEI/ARB and MRA should be used prior to commencement of the beta-blocker. In the euvolemic arm, ACEI/ARB should be commenced with beta-blockers with the option of adding an MRA following this. The guidelines suggest repeating cardiac imaging after 3–6 months of maximal tolerated dose. If HF persists and the ejection fraction is ≤40%, the ACEI/ARB should be swapped to an ARNI, this latter part of the algorithm reflects the inclusion criteria of the seminal PARADIGM-HF study[1] of sacubitril/valsartan in HFrEF compared to enalapril.

Since the Australian guidelines were written, much has occurred in the pharmacological therapy of HFrEF and the recently published Canadian and European guidelines and US expert consensus decision pathway reflect this.

The European guidelines recommend that four cornerstone therapies of HFrEF are commenced as soon as possible in all patients and they emphasise that all four are associated with rapid benefits and proven mortality and morbidity benefits. They recommend an ACEI (or ARNI as a replacement of ACEI), beta-blocker, MRA, and dapagliflozin† or empagliflozin†. These guidelines also give a weak recommendation for commencement of sacubitril/valsartan in ACEI-naïve/de novo patients with HFrEF.[2]

The Canadian guidelines similarly recommend four cornerstone therapies up front. Again, the beta-blocker, MRA, and SGLT2 inhibitor† as well as either an ARNI or an ACEI /ARB (then substituted by an ARNI).[3] These guidelines also support the use of an ARNI as first-line therapy in de novo patients with a weak recommendation.

Finally, the US expert consensus decision pathway is the most aggressive in terms of prescribing ARNIs, they recommend first-line therapy with an ARNI, beta-blocker, and diuretic and then split into streams (which can be followed in parallel), strongly recommending the addition of MRAs, SGLT2 inhibitors†, further diuretics or hydralazine and nitrates all in separate clinical scenarios.[4]

The standout difference between the three recent overseas guidelines and decision pathway and the Australian guidelines from 2018, are the strong support for SGLT2 inhibitors† and a varying degree of increased support for earlier use of an ARNI. Both of these significant changes reflect clinical studies performed and reported between 2018 and 2021.

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Expert's comments: Future of pharmacotherapy for HFrEF

Since the last iteration of the Australian guidelines for management of HF, there has been much progress in HFrEF pharmacotherapy.

The most striking advance in this short time is the movement of SGLT2 inhibitors† from a drug for type 2 diabetes, with the unexpected observation of reduced HF hospitalisation,[1-3] to a cornerstone therapy for HFrEF in reducing both morbidity and mortality.[4,5] Moreover, very recently, the EMPEROR-Preserved study[6] has shown a beneficial effect in HFpEF, which no pharmacological management has previously achieved. In both settings, the beneficial effect appears to manifest within weeks.[4-6]

There has also been evolution of the role of ARNIs in HFrEF. Sub-studies of the PARADIGM-HF trial[7] have demonstrated a rapid clinical benefit in the reduction in HF re-admission.[8,9] The safety and efficacy of ARNIs in acute decompensated HFrEF compared to ACEIs has been confirmed, with beneficial clinical effects on HF re-admission being seen at 8 weeks in PIONEER-HF.[10] Moreover, the PIONEER-HF and TRANSITION studies variably had between a quarter and a half of their population cohorts of HFrEF patients with de novo HFrEF or were ACEI/ARB naïve.[10,11] The outcome in these sub-groups were no different to that of the entire cohort, supporting the safety of ARNIs in the de novo or ACEI/ARB-naïve populations.

Together, the evolution of the SGLT2 inhibitors† and the further information supporting the use of ARNIs in HFrEF, added to the proven benefits of beta blockade and mineralocorticoid receptor antagonism, support the position that four different drug classes should be used in HFrEF. All four have proven benefits in mortality and morbidity and a rapid beneficial clinical impact. This raises the spectre of safety and timing of introduction and up-titration of four different drug classes in a HFrEF population that is often elderly and comorbid. Comorbidities, individual side effects of all four drug classes, and each patient's physiological parameters will need to carefully be considered by the prescribing physician. Parameters such as BP, potassium level, renal function, and diabetic and asthma status will all need to be considered for efficacy and safety. There is no getting away from the fact that pharmacological management of HFrEF will require significant clinical acumen, judgment, and finesse.

The 2018 Australian guidelines for management of HF were the first to recommend HFrEF treatment with ACEI/ARB, beta-blockers, and MRAs in HFrEF patients with an ejection fraction of 41–49%. The findings of the PARADIGM-HF and PARAGON-HF studies[7,12] when put together support a beneficial effect of the ARNIs in HF where the ejection fraction is 41–49%.[13] At the same time, the results of the EMPEROR programme[5,6] and SOLOIST-WHF trial[14] similarly support a beneficial effect of the SGLT2 inhibitors† in HF where the ejection fraction is 41–49%.

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Take-home messages

- Chronic HF is a common condition that causes considerable morbidity and mortality, resulting in the consumption of substantial healthcare resources.
- An ARNI or an ACEI, a beta-blocker and an MRA are foundational pharmacotherapy for HFrEF, with addition of an SGLT2 inhibitor† to further improve outcomes.
- In the Australian 2018 guidelines, an ARNI is recommended as second-line therapy in select populations; SGLT2 inhibitors† are not specified for HFrEF; and sGC stimulators¥ are not mentioned.
- Since publication of the Australian 2018 guidelines, new evidence and additional medications for chronic HF have been developed.
- ARNIs are recommended as first-line therapy in the US ACC 2021 decision pathway, CaReMe UK 2021 algorithm, Canadian 2021 guidelines update, and European 2021 guidelines.

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