A RESEARCH REVIEW™
SPEAKER SERIES

Treating Heart Failure in General Practice: What do I do next?

Making Education Easy 2022

About the speaker

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Dr Shakiya Ershad trained in Cardiology in Wellington followed by an imaging fellowship. She then undertook a cardiac transplant fellowship in Auckland and is now working as a heart failure and imaging cardiologist in Auckland. She is passionate about the care of heart failure patients.

Abbreviations used in this review

ACE = angiotensin-converting enzyme
AF = atrial fibrillation
ARB = angiotensin-receptor blocker
ARNI = angiotensin receptor II blocker – neprilysin inhibitor
CRT = cardiac resynchronisation therapy
CVD = cardiovascular disease
EF = ejection fraction
HF = heart failure
ICD = implantable cardioverter-defibrillator
LVEF = left ventricular ejection fraction
MRA = mineralocorticoid receptor antagonist
NT-proBNP = N-terminal pro b-type natriuretic peptide
NYHA = New York Heart Association
QoL = quality of life
RAAS = renin angiotensin aldosterone system
RRR = relative risk reduction
SGLT2 = sodium-glucose cotransporter 2
T2D = type 2 diabetes

This publication is a summary of a presentation from the virtual Goodfellow Symposium in March 2022. Treatments for heart failure are changing and evolving and primary care plays a crucial role in the management of heart failure patients. Dr Shakiya Ershad provided an overview of the guideline changes that have occurred, what steps to take next for your 'stable' HF patient and how primary care can keep these HF patients out of hospital and feeling better. The Goodfellow symposium is a primary care symposium designed for GPs, urgent care physicians, nurses, nurse practitioners and registrars. This resource was created with unconditional funding from Novartis NZ Ltd.

Introduction

The universal definition of HF was modified in 2021. HF occurs when a patient has objective evidence of cardiogenic pulmonary or systemic congestion, or elevated natriuretic peptide levels.[1]

Heart failure is caused by myocardial dysfunction that may be due to coronary artery disease/heart attack, high blood pressure, heart defects, damage to the heart muscle or arrhythmias. This results in diminished cardiac output and reduced renal blood flow. Renal-induced vasoconstriction and sodium retention subsequently increases blood pressure and causes oedema, which over time results in progressive HF.

Staging, assessment and diagnosis

Heart failure is staged as a continuum:[1]

- At risk of HF (stage A), e.g. patients with hypertension, CVD, or diabetes who require monitoring to prevent HF
- Pre-heart failure (stage B) - asymptomatic patients without signs of HF, but with evidence of structural heart disease, abnormal cardiac function or elevated natriuretic peptide
- Heart failure (stage C) – symptomatic patients and/or signs of HF caused by structural and/or functional cardiac abnormality
- Advanced HF (stage D) – severe symptoms requiring advanced therapies

The NYHA classification is used to describe the level of symptoms a patient is experiencing:[2]

I. Mild with no limitation during ordinary physical activity
II. Mild with slight limitation of physical activity
III. Moderate with marked limitation of physical activity
IV. Severe and unable to carry out any physical activity without discomfort

The majority of patients with chronic HF in general practice are mildly symptomatic, i.e. NYHA Class II.[3]

The diagnosis of HF was recently updated to include a new category of patients with mildly reduced EF who also require disease-modifying medication and support:[4]

- HF with reduced Ejection Fraction (HFrEF) = symptoms +/- signs* and LVEF ≤ 40%
- HF with mildly reduced Ejection Fraction (HFmrRF) = symptoms +/- signs* and LVEF 41-49%
- HF with preserved EF (HFpEF) = symptoms +/- signs* and LVEF ≥ 50%

*Signs may not be present in the early stage, particularly in HFpEF, or in optimally managed patients

There is a variety of causes for a reduced cardiac EF, however, the treatment goals remain the same.

Heart failure prognosis

All patients with HF have a poor prognosis, regardless of their symptoms.[5] There is a 50% mortality rate for patients with HFrEF within 5 years of diagnosis.[6] Within 3 years, 34% of patients with NYHA Class I and II symptoms and 42% of NYHA Class III and IV patients die.[5] A single hospitalisation due to HF increases a patient's risk of death by six-fold, compared to patients with HFrEF who have not been hospitalised.[7]

Heart failure prevalence

The burden of HF on the health system is considerable. In New Zealand, there was an estimated 75,000 adults with HF in 2018/19.[8] Māori are at 1.81 times greater risk of HF than non-Māori and Pacific Islanders are 1.92 times at greater risk than non-Pasifika. In 2017/18, there were 11,018 hospital discharges for HF with an average stay of 13.1 days.[9]

Causes and co-morbidities

Ischaemic heart disease and hypertension are the two main causes of HF in the developed world.[10] AF is commonly associated with HF and valve disease and cardiomyopathies can each account for up to 10% of HF cases.[10]

Heart failure progression

As HF progresses, the increasing frequency of acute events leads to higher rates of hospitalisation and an increased risk of mortality (**Figure 1**).[11,12]

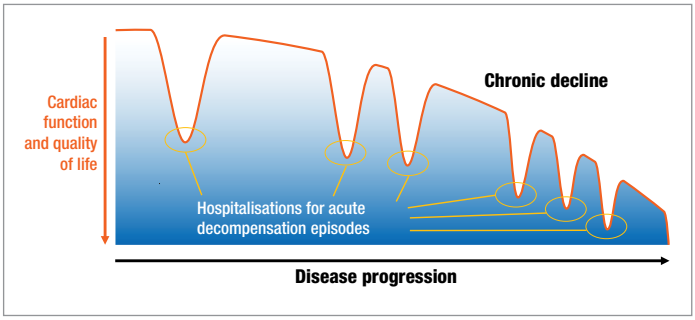


Figure 1: Heart failure progression, adapted from Gheorghiade (2005)[11]

Management objectives

The three management objectives for HF are:

1. Prognosis – reduce mortality
2. Morbidity - reduce hospitalisations, relieve symptoms and signs, improve QoL, eliminate oedema and fluid retention, increase exercise capacity, reduce fatigue and breathlessness, and provide end-of-life care
3. Prevention – avoid myocardial damage and limit progression, prevent remodelling of the myocardium, stop symptoms and fluid accumulation, prevent hospitalisation

Adverse cardiac remodelling

Adverse cardiac remodelling is the long-term changes that occur in response to the physiological adaptations resulting from cardiac damage. Chronic HF is characterised by neuroendocrine activation as the body attempts to maintain both the pump function of the heart and blood pressure to perfuse peripheral tissues. This induces maladaptive remodelling with a continuous deterioration in LV function. Pharmacological treatments aim to protect the heart from this neuroendocrine activation.

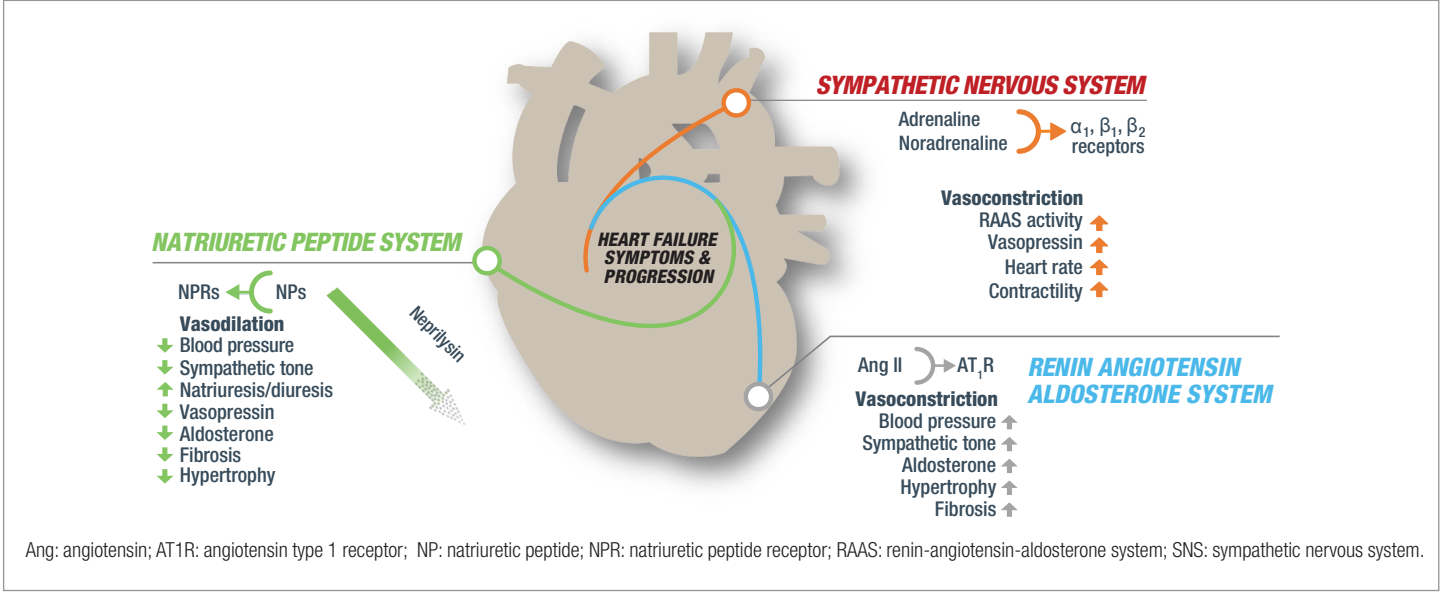
Cardiac damage is happening during HF even if it cannot be seen and the damage increases with every moment of HFrEF.[11,13] Adverse cardiac remodelling is a major factor in the progression of HFrEF and leads to poor outcomes.[14]

Neurohormonal pathways

The adverse cardiac effects of the sympathetic nervous system and RAAS activation are counteracted by a third neurohormonal pathway, the natriuretic peptide system (**Figure 2**).[15–19] The sympathetic nervous system and the RAAS are overactivated in HF and this maladaptive response underlies many of the pathophysiological processes contributing to disease progression.[17–19] The secretion of natriuretic peptides is a beneficial physiological response that decreases blood pressure and aldosterone, thereby decreasing the likelihood of hypertrophy and fibrosis.[15,16] Natriuretic peptides are broken down by neprilysin and blockade of this enzyme by an ARNI (sacubitril/valsartan, ENTRESTO®) is now a cornerstone of HF treatment.

Heart failure treatment recommendations

The American College of Cardiology (ACC) now recommends an ARNI ahead of an ACE inhibitor/ARB for the treatment of HFrEF (**Figure 3**).[20] The triad of ARNI/ACE inhibitor, beta-blocker and MRA is the cornerstone of HFrEF therapy.[4] An SGLT2 inhibitor is recommended as add-on therapy to ARNI/ACE inhibitor, beta-blocker and MRA; not before or as a replacement for any of these medicines.[4] If a patient is taking an optimal treatment regimen and is euvolemic, but their LVEF remains ≤ 35%, it may be appropriate to consider an ICD for the primary prevention of arrythmias if their QRS complex is < 130 ms, or a CRT if their QRS complex is ≥ 130 ms.



Ang: angiotensin; AT1R: angiotensin type 1 receptor; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system.

Figure 2: Neurohormonal pathways activated in heart failure

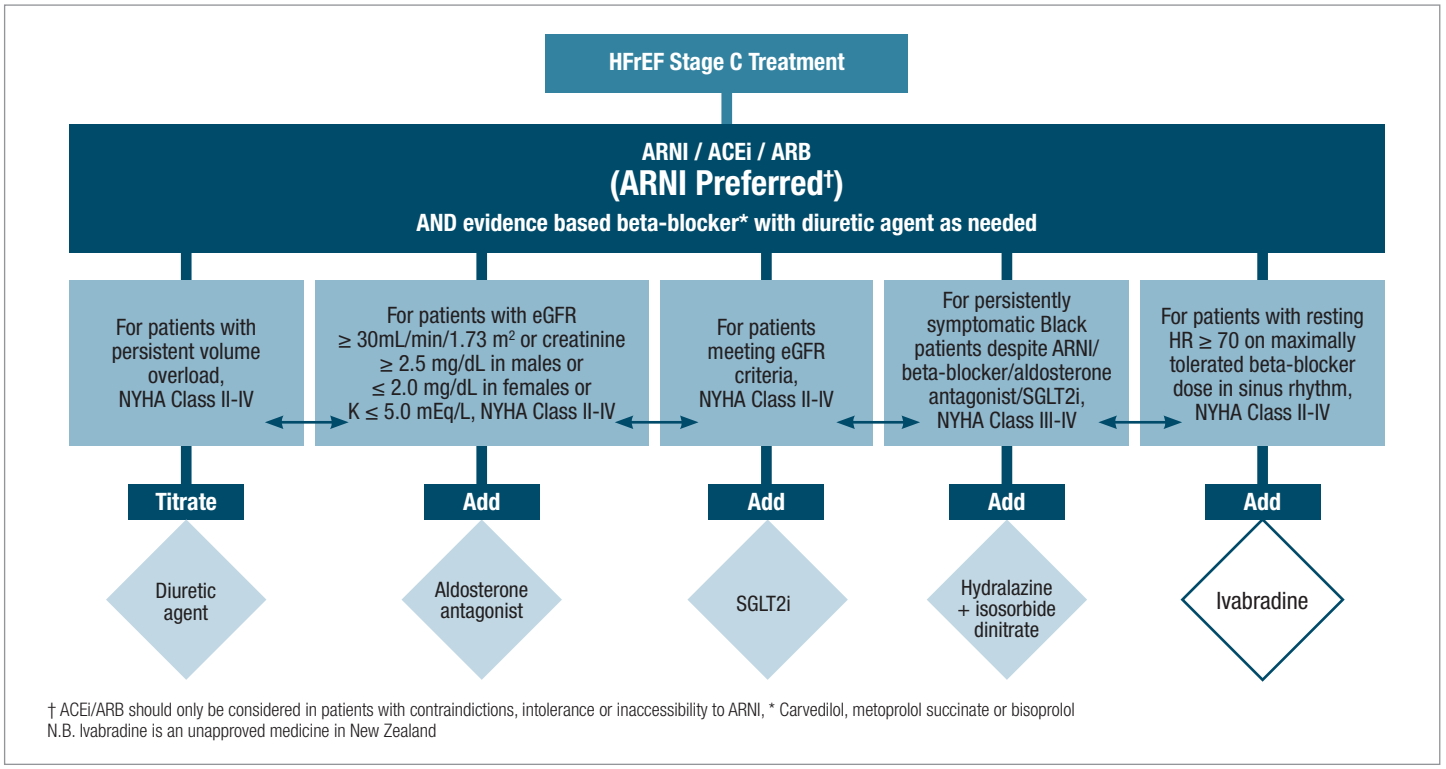


Figure 3: American College of Cardiology consensus decision pathway update, adapted from The Writing Committee.[20]

The four pillars of heart failure therapy

The treatment of HF has evolved away from the sequential initiation of medicines because they have an additive effect and some also have an early benefit, therefore medicines should be initiated early and in combination (**Figure 4**).[21]

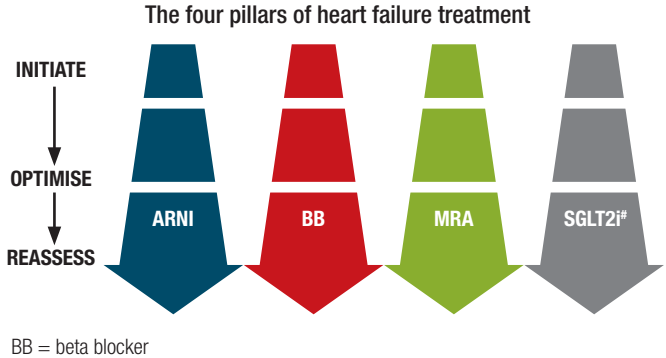


Figure 4: The four pillars of heart failure therapy, adapted from Straw[21]

If not, why not?

Dr Ershad recommends every patient with HF be assessed to confirm that they are each taking an ARNI, a beta-blocker, an MRA and an SGLT2 inhibitor at the maximum tolerated dose.

What is an ARNI?

Sacubitril/valsartan (ENTRESTO®) is a first-in-class angiotensin-receptor neprilysin inhibitor (ARNI). This medicine has been available internationally since 2015 and in New Zealand since 2018. Sacubitril/valsartan simultaneously delivers two active agents that provide:[22]

1. Neprilysin inhibition
2. Angiotensin-II receptor blockade

Evidence supporting the use of an ARNI

In patients with HFrEF, sacubitril/valsartan **replaces** the ACE inhibitor/ARB. This recommendation is based on the PARADIGM HF study (*n*=8,442) which was stopped early due to compelling evidence of efficacy and a reduction in cardiovascular mortality in patients taking sacubitril/valsartan, compared to enalapril.[23] This study found a 20% RRR of first HF hospitalisation or CV death associated with sacubitril/valsartan (p<0.001). There was also a 16% RRR in all-cause death with sacubitril/valsartan (p<0.001) and a 21% RRR in death due to worsening HF (p<0.034), compared to enalapril. The advent of ARNI therapy has revolutionised how HF patients are treated.

The multiple pathway approach of sacubitril/valsartan enhances the beneficial effects of the natriuretic peptide system, thereby increasing vasodilation and diuresis and reducing hypertrophy. At the same time, RAAS inhibition decreases vasoconstriction and reduces hypertrophy and retention of sodium and water.[24]

The PROVE-HF trial showed that sacubitril/valsartan reverses cardiac remodelling and improves cardiac structure and pump function in HFrEF patients.[25] The EVALUATE-HF trial demonstrated that sacubitril/valsartan rapidly improves remodelling and reduces NT-proBNP, compared to enalapril in HFrEF patients.[26] Beneficial cardiac remodelling may occur as early as six weeks after the initiation of sacubitril/valsartan. This emphasises how important it is to treat HF patients as early as possible.

The QoL for HF patients is also improved by sacubitril/valsartan. This improvement is sustained for up to 36 months and during the same period patients treated with enalapril experienced a decline in QoL.[27] The effect of sacubitril/valsartan on the physical and social activities of patients was equivalent to a difference of 9 years of ageing, compared to enalapril.[28]

Prescribing sacubitril/valsartan

Sacubitril/valsartan can be initiated under Special Authority Criteria by any relevant practitioner.[29] To be eligible, patients must have HF and be in NYHA/WHO functional Class II, III or IV, and have a documented LVEF ≤ 35% or **where an ECHO is not reasonably practical, the treating practitioner believes the patient would benefit from treatment**. Patients must also be receiving optimal standard chronic HF treatments to be eligible to meet the funding criteria.

Dr Ershad switches patients with HF from an ACE inhibitor/ARB to an ARNI once they have reached a mid-range dose. She also recommends starting most patients with known HF on an ARB, rather than an ACE inhibitor, to avoid the 36-hour wash-out period when switching from an ACE inhibitor to an ARNI.

The additive benefit of HF treatments

The mortality reductions associated with HF medicines are shown in **Figure 5A**. These benefits are additive and emphasise the importance of starting combination treatment early. **Figure 5B** shows that treatment with sacubitril/valsartan more than doubles the mortality benefit of an ACE inhibitor.

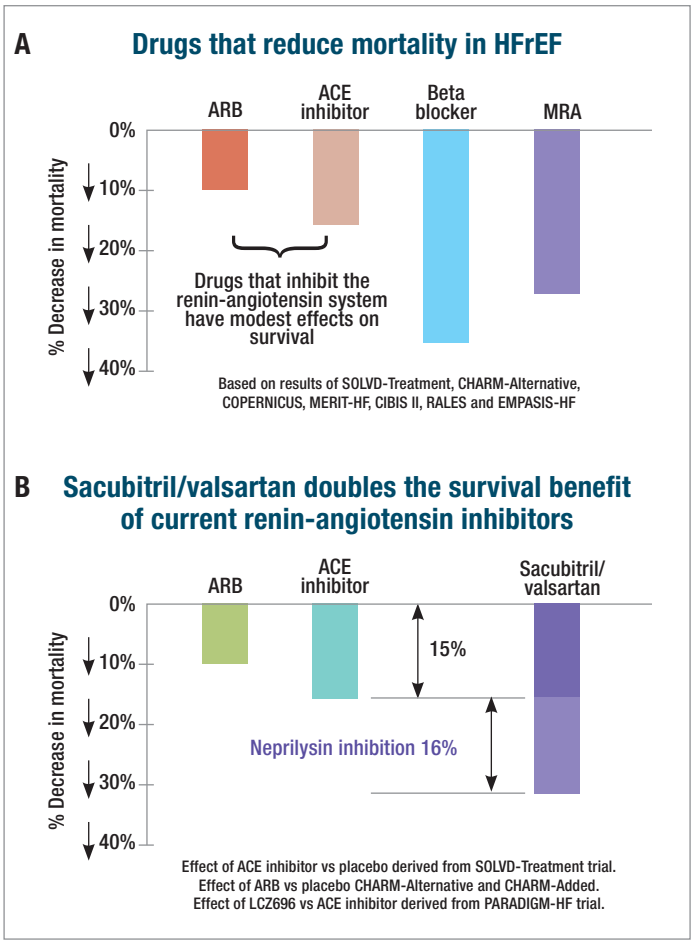


Figure 5: Mortality reductions associated with medicines in patients with HFrEF

Beta-blockers in heart failure

Beta-blockers reduce morbidity and mortality in HF by slowing the sinoatrial node located in the upper right atria, which initiates heartbeats, and by dilating arteries, thereby lowering blood pressure. Beta-blockers should be started in patients with HF at a low dose and slowly titrated to the maximum tolerated dose. Beta-blockers should be initiated alongside a RAAS agent in all patients with HFrEF, after a diuretic has reduced their fluid overload. Beta-blockers should not be initiated until the patient is euvolemic.

The cardio-selective beta-blockers, e.g. bisoprolol, carvedilol and metoprolol, have a greater affinity for beta$_1$-adrenoceptors and are less likely to cause bronchoconstriction in patients with asthma.[30]

Mineralocorticoid receptor antagonist in heart failure

The mode of MRA action is to block the effects of aldosterone released by the adrenal glands. This results in higher serum potassium and increased sodium excretion, resulting in decreased body fluid and lower blood pressure.

Low-dose spironolactone (25-50 mg) on top of background therapy decreases mortality and hospitalisations in chronic HF patients with moderate-to-severe symptoms and an LVEF ≤ 35%.[31]

An MRA is recommended in all patients with HFrEF and an LVEF ≤ 40% unless contraindicated or not tolerated, to decrease mortality and HF hospitalisations.[31] Spironolactone is generally initiated at 12-25 mg daily (depending on blood pressure) and the patient's renal function and potassium levels should be monitored. If a patient has experienced adverse effects from spironolactone, e.g. gynecomastia, eplerenone can be prescribed.

SGLT2 inhibitors in heart failure

Empagliflozin is indicated in patients with:[32]

- T2D to improve glycaemic control
- T2D and established CVD to reduce the risk of CV death
- HFrEF (adult patients NYHA Class II-IV), with or without T2D, to reduce the risk of HF hospitalisation and slow kidney function decline

Empagliflozin reduced the risk of major adverse cardiac and renal outcomes when added to inhibitors of the renin-angiotensin system, e.g. ARNIs, and beta-blockers, regardless of background therapy, with or without MRAs, and regardless of the presence or absence of diabetes.[33]

Empagliflozin is funded under Special Authority Criteria for patients with T2D. Dr Ershad recommends offering empagliflozin to HFrEF patients, although they will need to self-fund this treatment if they do not have T2D.

Loop/thiazide diuretics in heart failure

Loop diuretics, e.g. frusemide and thiazide, should be considered in patients with HF and symptoms or signs of congestion to improve symptoms and manage congestion.[31] Diuretics do not reduce mortality in HF. They should be started at a low dose and adjusted according to response. Diuretics are often initiated during the acute phase of HF to improve symptoms. Regular review is required after initiating a diuretic to ensure adequate management of congestion and to avoid over-diuresis.

Don't forget iron

Dr Ershad recommends performing a full blood count in all patients diagnosed with HF to assess their iron status. If the patient has HF and iron deficient anaemia, they will qualify for a subsidised iron infusion which should provide symptomatic benefit.

Case study – what can we do for our patient?

A 66-year-old male with HFrEF presents with fatigue and orthopnoea (**Table 1**). He reports feeling fatigued every day over the past 6-8 months, despite regular use of his continuous positive airway pressure device at night. He does not exercise much and often feels winded when walking up stairs. His medication has not changed recently and he reports good adherence to fluid and salt restriction. He denies any lower extremity oedema, abdominal distension, paroxysmal nocturnal dyspnoea, dizziness, and chest discomfort.

History	Medical history	Medications
• Retired car mechanic • Former smoker • Rarely drinks alcohol and denies illicit drug use • Mother had hypertension and diabetes • Father with history of stroke	• HFrEF diagnosed 3 years ago with LVEF on echocardiogram of 32% • Single chamber ICD (2010) • Non-obstructive coronary artery disease • Obstructive sleep apnoea • Hypertension • Obesity	• Enalapril 10 mg twice daily • Metoprolol CR 190 mg twice daily • Spironolactone 25 mg once daily • Frusemide 80 mg daily • Atorvastatin 40 mg once daily • Aspirin 100 mg once daily

Firstly, the patient's treatment should be assessed to ensure they are receiving the four pillars of HF therapy. Secondly, Dr Ershad recommends the following treatment changes:

1. Beta-blocker – ensure that a cardio-selective beta-blocker is prescribed and that it is slowly titrated to the maximum dose – DOSE DOES MATTER.
2. ACE inhibitor – switch to an ARNI as the EF is 32%. Remember the 36-hour washout period when switching from the ACE inhibitor to the ARNI and again, titrate to maximum dose – DOSE DOES MATTER.
3. MRA – ensure the dose is appropriate and he is taking the spironolactone regularly.
4. Diuretic – reduce or remove if the patient has no signs of congestion. This can help to increase the patient's blood pressure if it is low.
5. SGLT2 inhibitor- evaluate the patient for suitability, including if they meet Special Authority Criteria.

Following the switch from an ACE inhibitor to sacubitril/valsartan, the patient can expect:

- Reduced risk of sudden death or death due to worsening HF[34]
- Reduced risk of first HF hospitalisation[23]
- Improved QoL, including HF symptoms[27,28]
- Improved fitness and ability to participate in activities

Looking outside the circle

The optimal management of HF not only involves the four pillars of treatment, patients should also be assessed to determine if any medicines they are taking might be exacerbating their condition. For example, non-steroidal anti-inflammatory drugs may increase preload or afterload via a mismatch of vasodilatory and vasoconstrictive prostaglandins or $beta_2$-agonists or corticosteroids may counteract the action of beta-blockers.

TAKE-HOME MESSAGES

- There has been an evolution in the treatment of chronic HF
- General practitioners are ideally placed to intervene early in HF
- Rehospitalisation is a marker of HF decline
- Intervening early in the HF trajectory can impact the patient's long-term outcome and have a beneficial effect on the structure of their heart
- Titrated Guideline Directed Medical Therapies (GDMT) can maximise patient outcomes

Questions and answers

1. Would you prescribe an ARNI outside of the Special Authority Criteria?

Dr Ershad recommends an ARNI be prescribed according to the Special Authority Criteria. However, it is not necessary to wait until the patient has been titrated to their maximum dose of an ACE inhibitor/ARB before switching to an ARNI, particularly if they are young. Patients can generally be switched to an ARNI from a mid-dose ACE inhibitor or ARNI.

2. What guidance can you provide around starting a beta-blocker in a patient with asthma?

Firstly, a beta-blocker can be started in patients with chronic obstructive pulmonary disease. Secondly, beta-blockers are only a significant concern in patients with childhood asthma onset, i.e. truly reversible airways disease. In a patient with severe asthma, Dr Ershad does not recommend starting a beta-blocker, but if they have stable, well-controlled asthma a low-dose beta-blocker can be trialled. A cardio-selective beta-blocker such as bisoprolol would be a good option in this situation.

3. What guidance can you provide around the use of SGLT2 inhibitors in HF?

Dr Ershad is very positive about the benefits of SGLT2 inhibitors in HF patients. In New Zealand, there are two types of SGLT2 inhibitor available; empagliflozin is funded and dapagliflozin is not. These medicines have an early and late benefit in HF and reduce kidney disease progression.

4. Is a diuretic part of the four pillars of HF treatment or is it in addition to an MRA?

Diuretics do not make patients with HF live longer, but they do make them feel better by reducing fluid overload. Diuretics are therefore not part of the four pillars in terms of morbidity or mortality, but they are an extremely important part of treatment. Diuretics can be added to spironolactone, as spironolactone monotherapy is unlikely to produce sufficient diuresis for a patient with acute HF.

5. What guidance do you have for managing patients with HF with preserved ejection fraction?

Despite many studies attempting to improve the treatment of these patients, there is very little that can be done to reverse the pathology (fibrosis) underlying the condition. Management therefore focuses on symptom resolution and preventing hospitalisation. There is early evidence that ENTRESTO® may reduce hospital admissions for HF patients with preserved EF, although it does not appear to affect mortality. Empagliflozin has shown a reduction in HF hospitalisations compared to placebo and should be considered in patients with HFpEF with EF > 40%.

6. What advice can you provide for managing patients needing to access an echocardiogram?

This is a situation that is affecting the whole of New Zealand. Dr Ershad recommends waiting for some objective evidence that a patient has HFrEF before starting ENTRESTO®. Many of the other medicines used to treat HF can, however, be initiated before the patient undergoes an ECHO, including prescribing an ARB in preference to an ACE inhibitor. Noting patients with elevated BNP may reduce their waiting time for an echocardiogram when the referral is triaged.

7. What is the role of digoxin in HF treatment?

Dr Ershad still uses digoxin in HF patients, mainly those with AF. Digoxin is rarely prescribed to patients with HF only.

8. How should serum potassium levels be managed when patients are taking spironolactone?

This can be managed by reducing the MRA dose.

Entresto® (sacubitril/valsartan) is fully funded in New Zealand by Special Authority. Please refer to www.pharmac.govt.nz for the full criteria before prescribing.

INITIAL APPLICATION

Applications from any relevant practitioner. Approvals valid for 12 months.

Prerequisites (tick boxes where appropriate)

☐ Patient has heart failure

and

☐ Patient is in NYHA/WHO functional class II

or

☐ Patient is in NYHA/WHO functional class III

or

☐ Patient is in NYHA/WHO functional class IV

and

☐ Patient has a documented left ventricular ejection fraction (LVEF) of less than or equal to 35%

or

☐ An ECHO is not reasonably practical, and in the opinion of the treating practitioner the patient would benefit from treatment

and

☐ Patient is receiving concomitant optimal standard chronic heart failure treatments

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