Best Practice Message

November 2022

Entresto® and the future of heart failure treatment

Practice changing moments

- Heart failure disproportionately affects Māori and Pasifika males, however treatments such as Entresto® are currently underutilised.
- Consider reviewing patients for deconditioning, even if patient doesn't report dyspnoea or fatigue as they may be exhibiting activity avoidance behaviour.
- Consider all patients with Heart failure NYHA Class II/III for a switch to Entresto® if they meet the special authority criteria and treatment is not contraindicated.
- Patients receiving ACEi therapy prior to initiation will require a 36-hour washout period. This washout period is not required for patients on ARB therapy.

Introduction

It is estimated that 66,000 patients living with Heart failure in New Zealand. Māori and Pasifika males are almost 3 times as likely to develop Heart failure as non-Māori/Pasifika males[1].

Entresto® was first funded in New Zealand in 2018 for patients with chronic heart failure with reduced ejection fraction. Rates of prescribing in Hawke's Bay have lagged behind other areas. Uptake of this medication and rates of prescribing for Māori and Pasifika do not reflect the increased prevalence of heart failure in these populations. The reasons for this are likely complex.

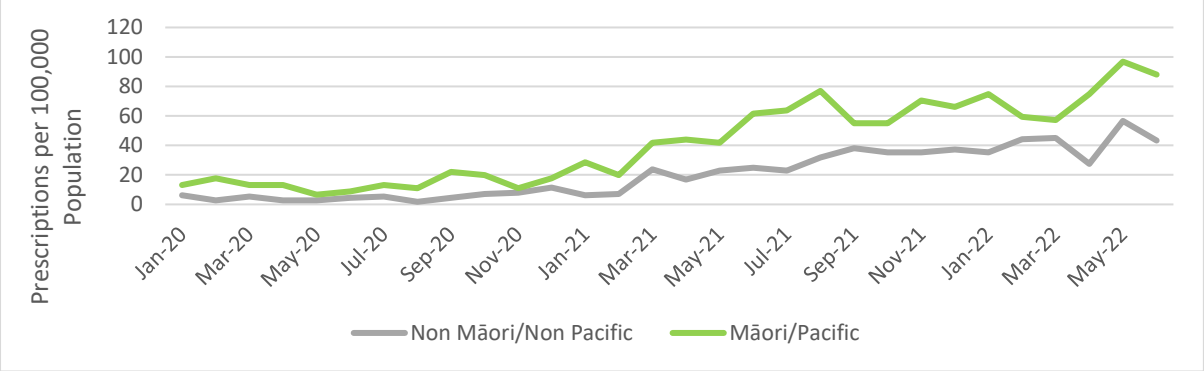

Figure 1. Prescribing rate for Entresto® in Hawke's Bay in Māori/Pasifika Patients vs Other ethnicities

Challenges in assessing Heart Failure New York Heart Association (NYHA) Class

A common issue with patients who have heart failure is an avoidance of activities which cause fatigue or dyspnoea leading to a new baseline quality of life. These patients may report that they are fine or have no symptoms of dyspnoea and being characterised as asymptomatic or NYHA Class I. Patients may also consider dyspnoea as a chronic symptom which is a normal aspect of their life[2]. It may take extra time to identify if patients are reporting no symptoms due to reduced activity, consider reviewing patients for deconditioning even if they report no dyspnoea or fatigue to assess if treatment needs to be escalated[3].

What is Entresto®?

Sacubitril + valsartan (Entresto®) is a first in class angiotensin receptor-neprilysin inhibitor (ARNI) combination which provides an added benefit over Angiotensin-Converting Enzyme inhibitor (ACEi) or Angiotensin II Receptor Blockers (ARB) therapy alone in patients with Heart Failure with reduced Ejection Fraction (HFrEF).

Entresto® achieved a 20% reduction in both cardiovascular mortality and heart failure hospitalisation relative to enalapril during the Paradigm-HF trial (NNT of 21 over 2.5 years)[4]. Similar improvements were seen using Entresto® over ACEi or ARB therapy in retrospective studies of real-world patients[5]. This caused international guidelines to change, with the American Heart Association recommending switching stable patients as well as those with chronic symptomatic HFrEF of NYHA Class II or III to Entresto® if they tolerate ACEi or ARB therapy[6].

What is the evidence for mid-range or preserved ejection fraction?

Given the benefit that is seen in patients with an ejection fraction below 35% the question has been raised, would we see a similar benefit in patients with a preserved ejection fraction (>49%) (HFpEF)? This has been explored with the PARAMOUNT trial, finding a reduction of NT-proBNP in patients treated with Entresto® however**, this did not translate to a clinical benefit**. The primary author continued this research with the PARAGON-HF trial which could not find a morbidity or mortality benefit of treating patients with HFpEF with Entresto[7]. However when patients were stratified by ejection fraction, therapeutic benefit remains for patients with a mildly reduced ejection fraction (41-49%)[8] (HFmrEF). However, use in patients with HFmrEF would not be funded.

Initiating Entresto® Therapy

Initial patient choice

With the benefits of Entresto® therapy over ACEi or ARB therapy, it is worth considering transitioning stable patients with NYHA class II/III HFrEF to Entresto®, if it is not contraindicated and the patient meets the PHARMAC Special authority criteria.

Special authority criteria

- Patients with heart failure NYHA class II-IV.*
- Patient is currently receiving concomitant optimal standard chronic heart failure treatments.
- Patient has documented LVEF of <35% (or if an ECHO is not reasonably practical and the treating practitioner believes the patient would benefit from treatment).

*While there is limited evidence of the use of Entresto® in patients with NYHA class IV, consider appropriateness to initiate therapy if it can be tolerated. Following the PIONEER-HF study[9] Entresto® has been shown to be able to be safely prescribed in patients hospitalized with acute decompensated heart failure. Patients may be started on this in hospital following decompensation events.

Starting dose

There are three strengths available of Entresto®; 24mg/26mg, 49mg/51mg, and 97mg/103mg. The starting dose of Entresto® depends on the previous therapy of ACEi or ARB, age and current SBP.

Patients requiring a lower dose include:

- ACEi or ARB Naïve or current dose of therapy is not >10mg Lisinopril or equivalent (see appendix 1)
- eGFR <30ml/min/1.73m^2
- Frail and/or Age ≥75
- Current SBP 100-110mmHg (Do not initiate if SBP <100mmHg)

Washout

It is important that patients who are switching from an ACEi have a 36-hour washout period prior to starting Entresto® to limit the risk of angioedema. This washout does not need to occur in patients switching from an ARB.

Dosing

- Standard dose; initiate 49mg/51mg dose twice daily, increasing to the target dose of 97mg/103mg twice daily after 2-4 weeks if tolerated.
- Lower dose; initiate on 24mg/26mg twice daily doubling the dose every 2- 4 weeks as tolerated to the same target dose of 97/103mg twice daily.

See NZF for more information.

Monitoring

Due to the impact on the renin angiotensin aldosterone system, monitoring is similar to an ACEi or ARB. It is important to monitor patients initiating Entresto® for:

- Hyperkalaemia
- Renal impairment
- Cough and angioedema.

Patients should also have their blood pressure and fluid status closely monitored during the initiation and titration phase. Consider if dose adjustments are required to diuretics (particularly if euvolaemic) and other agents not indicated for heart failure which reduce blood pressure to limit the risk of symptomatic hypotension at every dose adjustment.

	Before initiation	**During initiation and titration**	**Once Stable, repeat monitoring at:**			**Ongoing**	**Change in clinical condition or medication changes**
Blood pressure	Baseline	Every one to two weeks while titrating dose	6 weeks	3 months	6 months	6 monthly	Within 2 weeks
Renal Function and Electrolytes							

Entresto is generally well tolerated, however should the patient experience any adverse reaction, report this to CARM, as with any other medication.

Looking to the future - Sodium Glucose Transporter 2 inhibitors

There has been promising data showing a benefit using Sodium Glucose Transporter 2 inhibitor (SGLT2i) therapy in patients with or without diabetes. This has primarily come through the DAPA-HF (assessing dapagliflozin) and EMPEROR-REDUCED (assessing empagliflozin) trials which, when compared to placebo, found an approximate 25% reduction in HF hospitalisation or cardiovascular death irrespective of diabetes status[10–12]. These medications may also slow the rate of decline in eGFR[6]. This benefit was also explored in patients with HFpEF with promising results[13]. This has caused strong recommendations to use SGLT2i in patients with HFrEF, and consideration of use in patients with HFpEF in international guidelines[6]. These medications are currently only funded for diabetes management in New Zealand however this is an exciting area to watch.

Tools:

- NZF page for Entresto®
- NZF page for Chronic heart failure
- Heart Foundation hub of patient resources for Heart Failure

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Appendix 1 – approximate dose equivalencies to 10mg Lisinopril

	ACE inhibitors						**ARBs**	
	Cilazapril	**Lisinopril**	Perindopril	Enalapril	Quinapril	Ramipril	Losartan	Candesartan
Dose	2.5mg	**10mg**	4mg	10mg	10mg	2.5mg	50mg	8mg

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