

**ABSTRACT**

**In the last 40 years, pharmacological therapy for chronic heart failure has rapidly expanded beyond diuretics and digoxin. Standard pharmacological therapy includes beta blockers and renin-angiotensin-aldosterone system antagonists. Even with existing contemporary pharmacological therapy, which has substantially improved outcomes, prognosis is fairly poor. The treatment of heart failure continues to evolve with the integration of the results from landmark clinical trials into contemporary therapy. Development of novel therapeutic strategies for the treatment of this disease is crucial. Some of these new approaches will be briefly discussed.**

**Keywords:**

**Contemporary Pharmacological Therapy; Landmark Clinical Trials; Novel Therapeutic Strategies**

SFP2016; 42(2): 29-30

**PHARMACOLOGICAL THERAPY****1. Aldosterone Antagonist**

Guidelines have supported the use of aldosterone antagonists in systolic heart failure. The recommendations have been restricted to patients with moderate to severe heart failure (NYHA class III/IV) and those with clinical heart failure after myocardial infarction based on findings from RALES trial and EPHESUS trial respectively. There remains a data gap for patients with mild heart failure (NYHA class II). This gap has now been addressed by findings from the EMPHASIS-HF trial. In this study, 2737 patients with NYHA class II heart failure with an ejection fraction of no more than 35 percent were randomised to eplerenone (up to 50mg daily) or placebo, in addition to standard pharmacological therapy. The trial was stopped prematurely after a median follow-up period of 21 months. There was a 37-percent relative risk reduction for primary endpoint of cardiovascular death or hospitalisation for heart failure. Survival benefit was demonstrated with a relative risk reduction of 24 percent for death from any causes. Accordingly, guidelines updates have recommended eplerenone for patients with systolic heart failure who remained in NYHA class II despite receiving standard background therapy. One issue that is unanswered is the role of spironolactone (non-selective aldosterone antagonist) for such patients as it was not studied in the EMPHASIS-HF trial.

**2. Sinus Node Inhibitor**

Raised resting heart rate is a risk factor for mortality and cardiovascular outcomes in epidemiological and observational studies. Heart rate reduction has been postulated to be a

DAVID SIM KHENG LENG  
Senior Consultant, Cardiology,  
National Heart Centre Singapore

potential mechanism for the observed benefits with beta blockers. However, heart rate remains increased in most patients treated with beta blockers, which constitutes a need for new therapeutic strategies for heart rate reduction. Ivabradine is a specific inhibitor of the If current in the sinoatrial node and results in heart rate reduction with no other apparent direct cardiovascular effects. In the SHIFT trial, investigators studied the effects of ivabradine (up to 7.5mg bd) in 6558 patients who had symptomatic heart failure (NYHA class II-IV) and an ejection fraction of no more than 35 percent, were in sinus rhythm with heart rate 70 beats per min or higher, had been admitted to hospital for heart failure within the previous 12 months, and were on stable background treatment including beta blockers where tolerated. There was an 18-percent relative risk reduction for the primary end point of cardiovascular death or hospital admission for worsening heart failure. The effect was mainly driven by a relative risk reduction of 26 percent in hospital admissions for worsening heart failure. No significant reductions in all-cause or cardiovascular mortality were noted, although a reduction in deaths related to heart failure was suggested. Patients with lower baseline heart rates (<77 beats per min) and higher doses of beta blockers (at least half of recommended target dose) had diminished benefit of ivabradine.

**3. Angiotensin Receptor Neprilysin Inhibitor (ARNI)**

Another approach is to augment the renin-angiotensin system inhibition with inhibition via other pathways. Entresto (valsartan/sacubitril) is a new class of agents known as angiotensin receptor neprilysin inhibitor (ARNI). A twice-a-day tablet, it acts to enhance the protective neurohormonal systems of the heart (natriuretic peptide system) while simultaneously suppressing the harmful system (the renin angiotensin system).

Results from the 8442-patient PARADIGM-HF study showed, versus enalapril which is the current standard of care, Entresto:

- reduced the risk of death from cardiovascular causes by 20 percent
- reduced heart failure hospitalisations by 21 percent
- reduced the risk of all-cause mortality by 16 percent

Overall there was a 20-percent risk reduction on the primary endpoint, a composite measure of CV death or time-to-first-heart-failure hospitalisation.

Fewer patients on Entresto discontinued study medication for any adverse event compared to those on enalapril. The Entresto group had more hypotension and non-serious angioedema but less renal impairment, hyperkalemia and cough than the enalapril group.

Entresto has recently been approved for the treatment of heart failure with reduced ejection fraction (NYHA class II-IV) in several countries, including Singapore. As such, it will be important for physicians to fully understand how to effectively administer Entresto to ensure that patients receive the full benefit of the drug.

### **CARDIAC TRANSPLANT/VENTRICULAR ASSIST DEVICE**

Therapy for advanced heart failure patients involves a continuum of options. Despite advances in optimal medical therapy, a substantial number of patients progress to NYHA class III or Class IV, experiencing a dramatic reduction in quality of life. Cardiac transplantation is limited by the availability of donor hearts. Thousands of eligible patients face an extended waiting period associated with diminished functional capacity and high mortality rates; other patients are not candidates for transplantation.

With the new era of mechanical circulatory support, more patients who are refractory to optimal medical therapy can now significantly improve their quality of life and survival. The HeartMate II, a second-generation axial flow left ventricular assist device, has been extensively studied as a bridge to transplantation and destination therapy (i.e. for patients ineligible for cardiac transplant) for advanced heart failure.

To date, more than 20,000 patients have been implanted with HeartMate II worldwide. More than 90 percent of the patients on HeartMate II support reached the end point of transplantation, recovery of cardiac function, or mechanical circulatory support of at least 6 months. The majority of patients demonstrated vast improvement, progressing from severe heart failure symptoms even at rest (NYHA class III/IV) to being able to resume normal activities with little or no limitation (NYHA class I/II).

Due to limited donor availability, the introduction of HeartMate II has revolutionised the treatment of advanced heart failure in Singapore. Previous usage of a first-generation pulsatile left ventricular assist device was limited due to the smaller frames in our Asian population. Similar benefits observed in the clinical trials were also seen in our cohort of patients with more than 90 percent discharged home post-implantation despite majority of patients in cardiogenic shock requiring extracorporeal membrane oxygenation, intraaortic balloon pump, or inotropic support preoperatively.

### **CONCLUSION**

Heart Failure is a disease of epidemic proportions. The impact of this new epidemic poses a significant burden on the patients and the society. Many novel therapeutic approaches have emerged and are continuing to evolve, with many exciting possibilities for the future. Healthcare providers caring for heart failure patients require periodic review of all available treatment strategies in order to provide the best care for their patients.

### **REFERENCES**

1. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.
2. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, et al; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875-85.
3. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al; PARADIGM-HF Investigators. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993-1004.

---

### **LEARNING POINTS**

- **Heart Failure is associated with a high morbidity and mortality despite evidence-based pharmacological therapy.**
  - **Contemporary pharmacological therapy should be initiated in the early stages of heart failure.**
  - **Left ventricular assist devices have revolutionised the treatment of advanced heart failure.**
-