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SPEAKER SERIES

The "stable" heart failure patient and beyond

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About the speakers

Dr Pardeep Jhund

BSc MedSci (Hons), MBChB, MSc (Epidemiology), PhD (Cardiovascular epidemiology)

Dr Jhund is a Senior Clinical Lecturer at the British Heart Foundation (BHF) Glasgow Cardiovascular Research Centre, University of Glasgow, and Honorary Consultant Cardiologist at the Queen Elizabeth University Hospital, Glasgow, Scotland. He has an interest in the epidemiology of cardiovascular disease, with a specific focus on heart failure. The BHF Cardiovascular Research Centre has been at the forefront of clinical trials of sacubitril/valsartan, including the PARADIGM-HF trial, of which Dr Jhund has published a number of analyses.

The 2019 New Zealand Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand (CSANZ) was held in Wellington in June. Dr Pardeep Jhund from the University of Glasgow, Scotland, spoke at a breakfast symposium sponsored by Novartis (NZ) Ltd. This review summarises key points of Dr Jhund's presentation.

The symposium was opened by Associate Professor Gerry Devlin, current Medical Director of the Heart Foundation and Cardiologist at Gisborne Hospital. Associate Professor Devlin highlighted the burden of heart failure in New Zealand, and in particular the inequity of outcomes for Māori and Pacific patients with heart failure, who tend to die 10 years earlier than their European counterparts. With the inclusion of sacubitril/valsartan on the Pharmac schedule in October 2018, clinicians now have an opportunity to improve outcomes for all patients with chronic heart failure and reduced ejection fraction, he said.

Approval and reimbursement of the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan was based on the results of the landmark PARADIGM-HF trial, which found a 20% reduction in risk of cardiovascular death or heart failure hospitalisation with sacubitril/valsartan vs enalapril in patients with chronic heart failure and reduced ejection fraction (hazard ratio 0.80; 95% CI 0.73-0.87; p<0.001).[1]

Discordance between guidelines and clinical practice

European Society of Cardiology guidelines recommend a stepwise progression of treatments for patients with chronic heart failure and reduced ejection fraction, starting with an ACE inhibitor (or ARB) and a β-blocker, and adding a mineralocorticoid antagonist (MRA) if the patient is still symptomatic.[2] If the patient remains symptomatic after addition of the MRA, an ARNI is recommended in place of the ACE inhibitor/ARB.[2] Ivabradine and cardiac resynchronisation therapy (CRT) should also be considered for certain patients.[2] Diuretics should be used whenever the patient had signs and symptoms of congestion, and an ICD should be implanted in any patient with ejection fraction ≤35% despite optimal medical therapy or with a history of symptomatic ventricular tachycardia/fibrillation.[2] Guidelines from the American College of Cardiology/American Heart Association/Heart Failure Society of America,[3] and the National Heart Foundation of Australia and CSANZ, present similar recommendations.[4]

Dr Jhund suggested that in practice, clinicians are only following the first half of the guidelines, with most patients likely to receive ACE inhibitors and β-blockers, and approximately 50-60% receiving an MRA. In the PARADIGM-HF trial, 93% of patients were receiving a β-blocker and 56% were receiving an MRA.[1] However, despite the availability of sacubitril/valsartan in Europe for several years, this drug is still under-utilised, as are CRT and ICD. Dr Jhund questioned why this should be the case, and asked whether it was a result of the misguided perception that patients are "stable".

The myth of clinical stability in heart failure

Does "stable" mean no deterioration?

In medical terms, "stable" describes a patient who is not deteriorating in health, and therefore remaining in the same clinical state. Dr Jhund asked whether this was ever true of a patient with heart failure and reduced ejection fraction. He described the terminal decline typically seen in these patients, punctuated by multiple hospitalisations as well as outpatient and emergency department (ED) visits.[5]

In the EMPHASIS-HF trial, more than 25% of patients with mild symptoms of heart failure (NYHA class II) and reduced ejection fraction treated with the MRA eplerenone had been hospitalised for worsening heart failure or died of cardiovascular causes within 3 years.[6] In PARADIGM-HF, amongst patients hospitalised with worsening heart failure, 34% had ≥1 further hospitalisation after the first event, and 13% had ≥2 further hospitalisations.[7] One patient had a total of 18 hospitalisations.[7]

In patients treated with enalapril in the PARADIGM trial, the first manifestation of worsening disease state/instability was an ED visit in approximately 5% of patients and outpatient treatment in approximately 15% (most commonly an increase in diuretic dose >1 month).[8] In patients who had heart failure therapy intensified, 32% subsequently died, which was similar to the mortality rate seen in patients who had been hospitalised for worsening heart failure (see **Figure 1**).[9] Therefore a heart failure patient who is increasing their dose of diuretics at home is just as high risk as a patient who has been hospitalised, said Dr Jhund.

If intensification of therapy and ED visits were added into the PARADIGM trial composite endpoint of cardiovascular death or heart failure hospitalisation, the risk of an adverse outcome increased by 14%.[9] In summary, patients with heart failure and reduced ejection fraction who have mild symptoms are not stable and progress rapidly, said Dr Jhund, even on optimal medical therapy. In the PARADIGM-HF trial, more than 11% of enalapril-treated patients each year showed manifestations of worsening disease.[9]

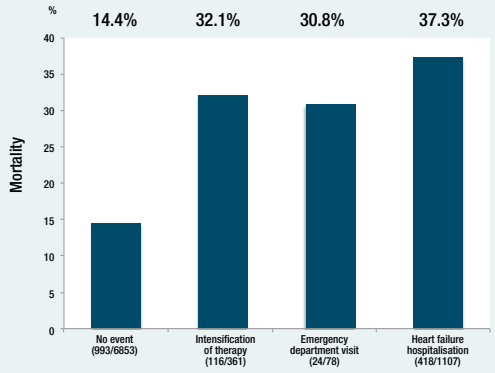


Figure 1. All-cause mortality after first manifestation of worsening disease state in patients treated with enalapril in the PARADIGM-HF trial.[9]

Benefit of sacubitril/valsartan on heart failure deterioration

Sacubitril/valsartan reduced the need for intensification of therapy by 18% (hazard ratio 0.82; 95% CI 0.62-1.08), and the need for an ED visit by 46% (hazard ratio 0.54; 95% CI 0.30-0.98), in the PARADIGM-HF trial.[9] The expanded composite endpoint of cardiovascular death, heart failure hospitalisation, ED visit or intensification of therapy was reduced by 21% (hazard ratio 0.79; 95% CI 0.73-0.86) with sacubitril/valsartan vs enalapril.[9]

Sacubitril/valsartan significantly reduced the cumulative incidence of heart failure hospitalisations compared with enalapril by 21-25% (rate ratios 0.75-0.79; 95% CI 0.66-0.90; all p<0.001), depending on the method used for counting recurrent events.[7]

Does "stable" mean low risk?

Dr Jhund suggested there is a mistaken belief amongst clinicians that patients in NYHA class II (as per 70% of the PARADIGM-HF trial population) are low risk. He stated that the NYHA classification system does not describe disease severity, it describes severity of symptoms.[10]

The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score has been developed by researchers at the University of Auckland, the Heart Foundation and the University of Glasgow, to identify high-risk heart failure patients.[11] Independent predictors of all-cause mortality included in the score are age, male sex, diabetes, chronic obstructive pulmonary disease, body mass index, current smoking, NHYA class, disease duration >18 months, creatinine level, systolic blood pressure, ejection fraction, ACE inhibitor/ARB use and β-blocker use.[11]

The median MAGGIC risk score in patients in the PARADIGM-HF trial was 20 (see **Figure 2**).[12] Patients with this score had a 40% chance of dying at 3 years.[12] Patients with a score of 30 had a 50% chance of dying.[12] Therefore this trial population, most of which were NYHA class II with mild symptoms, cannot be considered low risk.

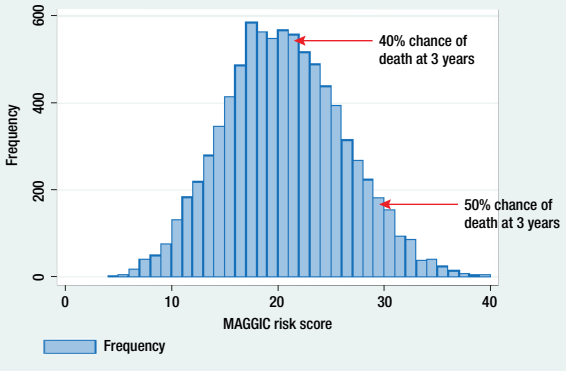


Figure 2. Frequency distribution of MAGGIC risk scores in the PARADIGM-HF trial.[12]

Benefit of sacubitril/valsartan across MAGGIC risk score quintiles

When patients from PARADIGM-HF were divided into 5 quintiles of MAGGIC risk score (4-15, 16-18, 19-21, 22-25 and 26-40), sacubitril/valsartan provided a consistent treatment benefit over enalapril for all-cause mortality, as well as cardiovascular death or heart failure hospitalisation, across all quintiles.[12] Treating 100 patients for 2 years with sacubitril/valsartan rather than enalapril would lead to 6 fewer deaths from any cause in the highest quintile of risk and 2 fewer deaths in the lowest quintile of risk.[12] Likewise, 7 fewer patients would experience cardiovascular death or heart failure hospitalisation in the highest quintile of risk and 3 in the lowest.[12]

Does "stable" mean the patient feels well?

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a heart failure-specific patient-reported measure of health status.[13] It assesses symptoms, physical limitations, self-efficacy, quality of life and social interference.[13] A 5-point change in overall KCCQ score corresponds to a 112-metre change in 6-minute walking distance, or a 2.5 ml/kg/min change in maximal oxygen consumption in patients with heart failure and reduced ejection fraction, and is considered to be clinically significant.[13]

In a post-hoc analysis of the PARADIGM-HF trial, including all patients with ≥1 KCCQ measurement and imputing a score of 0 for those who died, at least 35% of patients had a ≥5-point deterioration in KCCQ clinical summary score at 12 months, regardless of treatment given (see **Figure 3**). By 24 months, at least 43% had a ≥5-point deterioration. However at all time points, significantly fewer patients treated with sacubitril/valsartan had a ≥5-point deterioration in KCCQ clinical summary score compared with those treated with enalapril (p≤0.01).

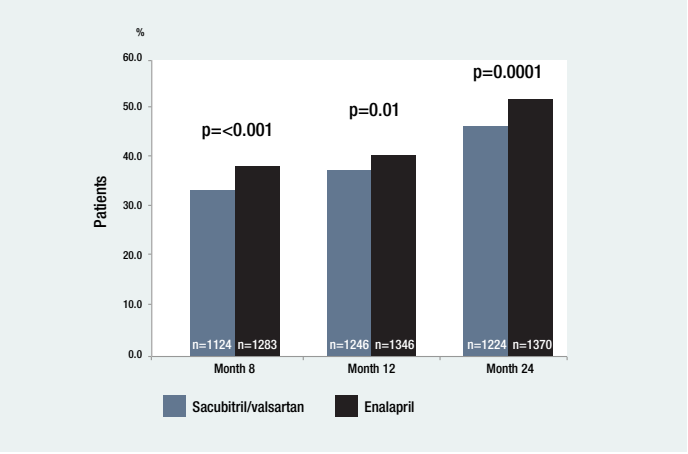


Figure 3. Patients with a ≥5-point deterioration in KCCQ clinical summary score in the PARADIGM-HF trial.

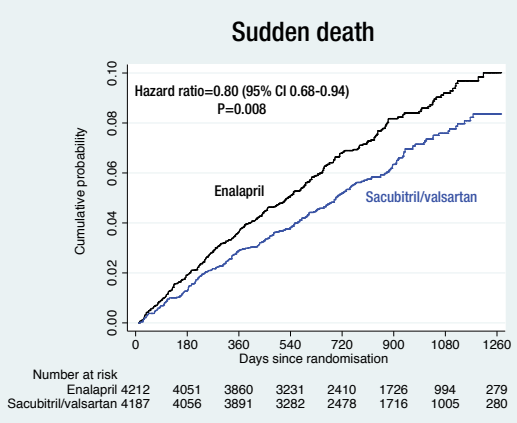
Does "stable" mean patients are not likely to die?

The two major modes of death in heart failure are sudden death and death due to worsening heart failure.[14] Patients in NYHA class II are more likely to experience sudden death than death due to worsening heart failure.[14] In PARADIGM-HF, 33% of the first primary endpoints were cardiovascular deaths, of which 61% were sudden, meaning there was no chance to intervene.[14]

Sacubitril/valsartan had a similar effect on the two major modes of death in the PARADIGM-HF trial, reducing the risk of sudden death and death due to worsening heart failure by 20% (hazard ratio 0.80; 95% CI 0.68-0.94; p=0.008) and 21% (hazard ratio 0.79; 95% CI 0.64-0.98; p=0.034), respectively, vs enalapril (see **Figure 4**).[14]

"Stable" suggests you have time

Dr Jhund emphasised that the risk of sudden death in patients with heart failure means clinicians can't afford to wait to provide optimal medical therapy. He believes it is important to do everything possible *today* to improve their patient's prognosis. As well as treatment with sacubitril/valsartan, this means up-titrating the β-blocker, making sure the patient is receiving an MRA, using other drugs as necessary, and also utilising CRT and ICD. In PARADIGM-HF, sacubitril/valsartan had significantly reduced the risk of heart failure hospitalisation compared with enalapril after just 30 days (hazard ratio 0.60; 95% CI 0.38-0.94; p=0.027).[8]



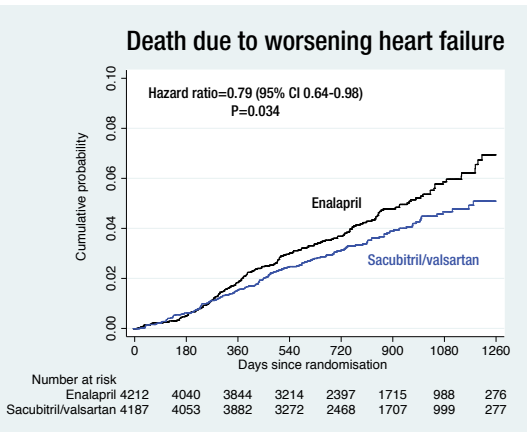


Figure 4. Major modes of death in the PARADIGM-HF trial.[14]

What about hospitalised patients?

The recently published PIONEER-HF and TRANSITION trials have provided important safety data supporting the initiation of sacubitril/valsartan in hospitalised patients with acute decompensated heart failure.[15,16]

Dr Jhund would now start treatment with sacubitril/valsartan rather than an ACE inhibitor in most patients with acute decompensated heart failure. Patients are in safe environment where they are being constantly monitored, and blood tests can easily be performed every day. Starting treatment with sacubitril/valsartan earlier means the patient does not have to wait as long to receive optimal medical therapy. Dr Jhund acknowledged that it may take some time before the PIONEER-HF and TRANSITION trial results are incorporated into treatment guidelines.

PIONEER-HF trial

The randomised, double-blind PIONEER-HF trial investigated the efficacy and safety of sacubitril/valsartan compared with enalapril in 881 hospitalised patients with acute decompensated heart failure.[15] Patients had an ejection fraction ≤40%, elevated NT-proBNP concentration, systolic blood pressure ≥100 mm Hg, no increase in the dose of intravenous diuretics and no use of intravenous vasodilators in the preceding 6 hours, and no use of intravenous inotropes in the preceding 24 hours.[15] At the time of hospital admission, 52% of patients were not receiving treatment with an ACE inhibitor or ARB.[15]

There was a 29% reduction in the primary endpoint of time-averaged proportional change in NT-proBNP concentration from baseline at weeks 4 and 8 with sacubitril/ valsartan vs enalapril (ratio of change 0.71; 95% CI 0.63-0.81; p<0.001).[15] The rate of heart failure rehospitalisation was also reduced with sacubitril/valsartan vs enalapril, but this was an exploratory endpoint only.[15] Importantly, there were no significant differences in key safety outcomes of worsening renal function, hyperkalaemia and symptomatic hypotension between the sacubitril/valsartan and enalapril groups (see **Table 1**).[15]

	Sacubitril/valsartan (n= 440)	Enalapril (n = 441)	Relative risk (95% CI)
Worsening renal function	60 (13.6%)	65 (14.7%)	0.93 (0.67-1.28)
Hyperkalaemia	51 (11.6%)	41 (9.3%)	1.25 (0.84-1.84)
Symptomatic hypotension	66 (15.0%)	56 (12.7%)	1.18 (0.85-1.64)

Table 1. Key safety outcomes in patients with acute decompensated heart failure in the PIONEER-HF trial.[15]

TRANSITION trial

The TRANSITION trial investigated tolerability and the optimal time point for initiation of sacubitril/valsartan in 1002 patients hospitalised with acute decompensated heart failure.[16] All patients had ejection fraction ≤40% and systolic blood pressure ≥100 mm Hg, and had not received intravenous diuretics in the preceding 24 hours.[16] Patients were stratified according to preadmission use of ACE inhibitors/ARBs, and were randomised to receive sacubitril/valsartan either ≥12 hours before discharge or 1-14 days after discharge.[16]

There was no difference between groups in the proportion of patients who achieved the 97/103 mg twice daily target dose of sacubitril/valsartan at week 10, with 45.4% of patients in the pre-discharge group and 50.7% of patients in the post-discharge group achieving the target dose (relative risk 0.90; 95% CI 0.79-1.02; p=0.099).[16]

Predictors of titration success were age <65 years, systolic blood pressure ≥ 120 mm Hg at baseline, history of hypertension, no prior history of heart failure, no atrial fibrillation at baseline, estimated glomerular filtration rate ≥60 ml/min/1.73 m^2 at randomisation, and a sacubitril/valsartan starting dose of 49/51 mg twice daily. Assignment to pre- or post-discharge initiation of sacubitril/valsartan, or prior use of an ACE inhibitor/ARB, had no impact on titration success.[16]

There were no differences in safety outcomes between patients who started sacubitril/valsartan before discharge and those who started after discharge (see **Table 2**).[16]

	Sacubitril/valsartan		
	predischarge (n = 495)	post-discharge (n = 496)	Relative risk (95% CI)
Hyperkalaemia	56 (11.3%)	56 (11.3%)	1.002 (0.71-1.42)
Hypotension	63 (12.7%)	47 (9.5%)	1.343 (0.94-1.92)
Cardiac failure	35 (7.1%)	42 (8.5%)	0.835 (0.54-1.28)
Dizziness	28 (5.7%)	21 (4.2%)	1.336 (0.77-2.32)
Peripheral oedema	17 (3.4%)	24 (4.8%)	0.710 (0.39-1.30)
Renal impairment	25 (5.1%)	16 (3.2%)	1.566 (0.85-2.90)
Diarrhoea	12 (2.4%)	24 (4.8%)	0.501 (0.25-0.99)
Urinary tract infection	21 (4.2%)	14 (2.8%)	1.503 (0.77-2.92)

Table 2. Adverse events with a frequency of ≥2% in patients with acute decompensated heart failure in the TRANSITION trial.[16]

Is my patient a candidate for sacubitril/valsartan?

The belief that patients in the clinic are not suitable candidates for sacubitril/valsartan does not appear to hold true, as Dr Jhund and colleagues have shown that the majority of real-world patients with heart failure and reduced ejection fraction would be eligible for treatment with sacubitril/valsartan.[17] They used data from the Swedish Heart Failure Registry to examine eligibility, using entry criteria of the PARADIGM-HF trial.[17] Patients were considered potentially eligible for sacubitril/valsartan if they were not hospitalised, were in NYHA class II-IV, had ejection fraction ≤40%, and had been prescribed an ACE inhibitor or ARB at a dose equivalent to enalapril ≥10 mg/day.[17]

Out of 12,866 patients in NYHA class II-IV with ejection fraction ≤40%, 9577 had been prescribed enalapril ≥10 mg/day or equivalent.[17] Complete additional data were available for 32.4% of these patients, of whom 75.5% were potentially eligible for sacubitril/valsartan treatment. The most common reason for ineligibility was a low natriuretic peptide level (14.9%).[17]

TAKE-HOME MESSAGES

- Patients with heart failure and reduced ejection fraction are not "stable"
  - They will experience a deterioration in their symptoms
  - They are not low risk
  - They are at substantial risk of sudden death
- We have safety data to support use of sacubitril/valsartan in the hospitalised setting and in treatment-naïve patients
- Most patients are eligible for evidence-based therapies; it is up to clinicians to provide them.

Questions and answers

Assuming heart failure patients are not "stable", who should manage these patients?

Dr Jhund said that the management of patients with heart failure is complex and challenging, and suggested that care could be moved from GPs to specialists. However, a GP in the audience pointed out that patients manage their heart failure, not physicians. Patients value the relationship they have with their GP, and this can positively affect treatment adherence. She suggested that GPs could be supported with expert advice, rather than transferring care to specialists.

If your patient developed hyperkalaemia while receiving sacubitril/valsartan and spironolactone, would you stop the spironolactone or the sacubitril/valsartan?

Dr Jhund said there was not a simple answer to this question, and such scenarios highlighted why he believed heart failure should be under specialist care. A range of factors need to be considered, including the patient's renal function and fluid levels, how long the patient has been receiving both treatments, and whether doses have recently been up-titrated. Dr Jhund noted that over time, potassium levels in patients receiving sacubitril/valsartan are lower than in those receiving an ACE inhibitor. The risk of serious hyperkalaemia with sacubitril/valsartan plus an MRA is the same as with an ACE inhibitor alone, he said.

Can you comment on adherence with sacubitril/valsartan?

We can't deduce anything from the PARADIGM-HF trial about adherence with sacubitril/valsartan in the real-world setting, Dr Jhund said. However, in the UK most patients with heart failure and reduced ejection fraction have historically been treated with twice-daily enalapril, so he has not experienced problems with switching to twice-daily sacubitril/valsartan. He said strategies such as using blister packs can be used to improve overall adherence with heart failure medication.

Would you give sacubitril/valsartan to a patient with a systolic blood pressure of around 90 mm Hg?

Dr Jhund said that the patient's renal function should always be considered. However if he would give the patient an ACE inhibitor or ARB, he would give them sacubitril/valsartan.*

*Patients with systolic blood pressure <100 mm Hg at the time of sacubitril/valsartan initiation have not been studied in clinical trials, therefore the use of sacubitril/valsartan is not recommended for these patients.

Are patients who can't be up-titrated to the target maintenance dose of sacubitril/valsartan because of hypotension receiving the same benefit as they would on an optimal ACE inhibitor/ARB dose?

We don't have the answer to this question, Dr Jhund said. However, he noted that there are often other factors responsible for the hypotension. Fluid status is crucially important, and reducing the dose of diuretics may allow the dose of sacubitril/valsartan to be up-titrated. Dr Jhund would rather look at these factors and work towards up-titrating sacubitril/valsartan than switch patients back to an ACE inhibitor or ARB.

In patients who develop hypotension whilst receiving sacubitril/valsartan, would you reduce the dose to once daily at night?

Dr Jhund noted that for neprilysin inhibition to be maintained over a 24-hour period, sacubitril/valsartan needs to be given twice daily. For patients who can't tolerate sacubitril/valsartan, Dr Jhund would switch back to an ACE inhibitor or ARB, but not before considering other factors responsible for adverse events.

Do you use natriuretic peptide levels to monitor patients receiving sacubitril/valsartan?

While natriuretic peptide levels are useful for diagnosis, Dr Jhund doesn't assess them during treatment with sacubitril/valsartan as it wouldn't change his management decisions.

Can you comment on use of SGLT-2 inhibitors in patients with heart failure?

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are a new class of oral hypoglycaemic agents which are available in the UK and US but are not yet funded in New Zealand. Dr Jhund has used SGLT-2 inhibitors to treat type 2 diabetes in patients receiving sacubitril/valsartan for heart failure. It is important to carefully monitor fluid status in patients receiving these two drugs concomitantly, as SGLT-2 inhibitors can have a diuretic effect. While there are some preliminary data to indicate a role for SGLT-2 inhibitors in the treatment of heart failure itself, the results of ongoing randomised controlled trials are needed to confirm this. At present, Dr Jhund would choose guideline-approved treatments for heart failure.

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