CARDIOLOGY Rounds®

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Practical Applications of Angiotensin Receptor-Neprilysin Inhibition in Patients with Heart Failure and Reduced Ejection Fraction

By JONATHAN G. HOWLETT, MD, FRCPC, ANIQUE DUCHARME, MD, MSc, FRCPC, and GORDON MOE, MD, FRCPC

The combined angiotensin receptor and neprilysin inhibitor sacubitril/valsartan increases survival, reduces hospitalization, and improves quality of life and the feeling of well-being compared to the angiotensin-converting enzyme inhibitor enalapril in patients with heart failure and reduced ejection fraction. Due to its multiple modes of action and the complexity of the study design of its landmark trial PARADIGM-HF, the use of sacubitril/valsartan may at times appear tricky to physicians, particularly on initiation. In this issue of *Cardiology Rounds*, using case illustrations, the practical strategies to maximize the benefits and prevent potential complications when using sacubitril/valsartan will be discussed.

More than 600 000 Canadians are living with heart failure (HF), with 50 000 new cases diagnosed each year.[1] At present, 50% of patients will die from the disease within 5 years, representing 9% of all deaths in Canada, or approximately 22 000 deaths annually.[2] HF is also the second leading cause of hospitalization in Canada for patients older than 65 years.[3] In 2012, the direct costs of treating HF were estimated at $2.89 billion per year.[4]

While it has been possible to slow the progression of HF symptoms with pharmacological therapies and lifestyle changes, which can extend and improve quality of life, there have been no major advances in the treatment of HF for several years. Sacubitril/valsartan, commercially known as Entresto®, is a first-in-class angiotensin receptor neprilysin inhibitor (ARNi). A twice-a-day tablet, sacubitril/valsartan enhances the protective natriuretic peptide system while concurrently suppressing the harmful renin angiotensin aldosterone system.[5] Sacubitril/valsartan was approved by Health Canada based on the results of the landmark Prospective Comparison of ARNi with ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial.[6]

In brief, PARADIGM-HF[6] was a double-blind trial, in which 8442 patients with New York Heart Association (NYHA) class II-IV HF and a reduced (≤40%) ejection fraction (HFrEF) were randomized to either sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily. The primary outcome was a composite of death from cardiovascular (CV) causes or hospitalization for HF; however, the trial was designed to detect a difference in the rates of CV death. PARADIGM-HF was stopped prematurely – median follow-up of 27 months – after the boundary for an overwhelming benefit with sacubitril/valsartan was achieved. Results at the time of trial cessation demonstrated that sacubitril/valsartan was associated with a 20% risk reduction in the primary endpoint, which had occurred in 21.8% of patients in the sacubitril/valsartan group and in 26.5% of the enalapril group; the hazard ratio of the primary outcome in the sacubitril/valsartan group was 0.80 (95% confidence interval 0.73–0.87; $P<0.001$).

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Table 1: Outcomes and markers of worsening of heart failure in which sacubitril/valsartan performed better than enalapril

- Symptomatic deterioration
- Premature death, either suddenly or from worsening HF
- Biomarker evidence of cardiac wall-stress and myocyte injury
- Need to intensify oral therapy/addition of intravenous (IV) therapy
- Emergency department visits
- Hospital admission
- Transfer to the intensive care unit when admitted
- Need for IV therapy or devices/surgery for worsening/end-stage HF (not statistically significant)

Treatment with sacubitril/valsartan was also associated with the following:

- 20% reduction in the risk of death from CV causes (13.3% versus 16.5% with enalapril; $P<0.001$)
- 16% reduction in the risk of all-cause mortality (17.0% versus 19.8% with enalapril; $P<0.001$)
- 21% decrease in HF hospitalizations (12.8% versus 15.6% for enalapril; $P<0.001$)

The impact of sacubitril/valsartan on clinical status has also been published.[7-10] The likelihood of the outcomes and markers of nonfatal clinical worsening as shown in Table 1 were lower in patients taking sacubitril/valsartan compared with enalapril.

A *post hoc* analysis of PARADIGM-HF evaluated the changes in health-related quality of life (HRQoL) scores, according to the Kansas City Cardiomyopathy Questionnaire, in patients who were and were not hospitalized due to HF and according to medical treatment.[11] The decline in HRQoL associated with HF hospitalization among patients taking sacubitril/valsartan was smaller compared to those taking enalapril (-5.11±1.62 versus -10.77±1.15, respectively). A second *post hoc* analysis of the overall study population showed an association between decline in HRQoL scores and increased risk of CV death and HF hospitalization.[12] Sensitivity analyses have also demonstrated sacubitril/valsartan may remain cost effective versus enalapril.[13,14]

As a result of these accumulated trial evidence, clinical practice guidelines in HF have recommended the use of sacubitril/valsartan in place of angiotensin-converting enzyme (ACE) inhibitors in patients with HFrEF.[15-17] However, the drug has multiple modes of action and the complex design of PARADIGM-HF may potentially make it tricky to use by the practicing physician. The following clinical cases are intended to present practical aspects relating to the use of sacubitril/valsartan.

Case 1

A 65-year-old male with a history of ischemic cardiomyopathy, coronary artery bypass graft surgery in 2011, and insertion of an implantable cardioverter-defibrillator for primary prevention in 2007, is followed at the HF clinic. He has a longstanding history of poorly controlled diabetes mellitus, which is now treated with insulin. His diabetes is complicated by retinopathy, for which he has undergone laser treatment 4 times, and chronic kidney disease (estimated glomerular filtration rate [eGFR] 45 mL/min/1.73 m^2). He also has dyslipidemia, hypertension, and obesity. Moreover, he suffered a stroke in 2006, presumably embolic from an apical thrombus and a left ventricular (LV) aneurysm, and has been on an oral anticoagulant ever since. A recent echocardiogram demonstrated a dilated left ventricle (61/50 mm) with a LVEF of 32%, and mild mitral and tricuspid regurgitation, as well as moderate pulmonary hypertension (estimated systolic pulmonary artery pressure of 55 mmHg).

The patient remained symptomatic with NYHA Class III symptoms despite being on maximally tolerated doses of guideline-recommended pharmacological therapy: bisoprolol 5 mg once daily with a heart rate (HR) of 55 beats/min, lisinopril 20 mg once daily, eplerenone 25 mg once daily (dose increases limited by hyperkalemia), and furosemide 60 mg once daily. In the last 3 months he experienced 2 episodes of acute decompensated HF requiring the administration of intravenous diuretics at the HF clinic. His vital signs were stable, with a blood pressure (BP) of 104/60 mmHg and HR of 55 beats/min. Lisinopril was switched to sacubitril/valsartan 24/26 mg twice daily.

The patient initially developed mild dizziness and deterioration of his renal function; serum creatinine rose from 145 mmol/L to 179 mmol/L. His diuretic regimen was then decreased to furosemide 40 mg once daily, the symptoms resolved, and the creatinine improved. When seen 2 months after initiation, the patient was euvolemic

with NYHA Class II symptoms and his N-terminal pro b-type natriuretic peptide (NT-proBNP) level had dropped from 2588 to 1645 pg/mL, but he complained of multiple hypoglycemic episodes. His hemoglobin A1C decreased from 8.1% to 7.5%, prompting the need to decrease his insulin doses by 50%. We increased his sacubitril/valsartan to 49/51 mg twice daily and the patient was seen monthly thereafter for further dose optimization.

This case illustrates several features that may be encountered with the initiation of sacubitril/valsartan. Key learning points include the following:

1. Dizziness after sacubitril/valsartan initiation is not infrequent and generally does not reflect intolerance to the new agent but rather the need to reduce the dose of diuretics.[6] This is caused by the vasodilatory action of angiotensin receptor blockade (ARB) with valsartan, combined with the diuretic action of neprilysin inhibition with sacubitril. It is, therefore, important to advise the patient beforehand. Alternatively, one could have decreased the dose of furosemide upfront concurrently; however, in this case we were reluctant to do so because of his recent decompensation. Starting at low dose with more gradual increase may have mitigated this situation.
2. As usual, deterioration of renal function must be evaluated in the clinical context. While our patient had 2 recent episodes of acute decompensation with development of a cardiorenal syndrome, this was not the case after sacubitril/valsartan initiation, as it was probably due in part to volume contraction.
3. In obese hypertensive patients, sacubitril/valsartan, but not amlodipine, is associated with a significant increase in insulin sensitivity index.[18] Consequently, we believed that this was not a mere drug interaction phenomenon but due to the peculiar effect of sacubitril; neprilysin is ubiquitously expressed, even in adipocytes, and its plasma activity correlates with measures of obesity and insulin resistance.[19] Furthermore, angiotensin II promotes insulin resistance, and angiotensin 1 receptor blockade modestly improved insulin sensitivity and pancreatic beta-cell function in humans.[20]

Failure to recognize the above issues could have led to unnecessary cessation of the new drug and potentially hasten HF progression.

Case 2

A retired 69-year-old male smoker with nonischemic dilated cardiomyopathy and a cardiac resynchronization therapy defibrillator implantation in 2012 was seen for the first time at the HF clinic in early 2016. He has a longstanding history of type II diabetes mellitus and chronic kidney disease (eGFR 33 mL/min/1.73 m^2), hypertension, benign prostatic hyperplasia, osteoarthritis, and peripheral vascular disease. When first diagnosed in 2014 the patient was treated with furosemide, carvedilol 25 mg twice daily, and spironolactone 12.5 mg once daily. At some point in the past his spironolactone was stopped. The patient was also taking sitagliptin, metformin, and doxazosin, and occasionally took over-the-counter nonsteroidal anti-inflammatory agents (NSAIDs) and glucosamine. A recent echocardiogram showed a dilated left ventricle (57/49 mm) with a LVEF of 26% (initially 15% in 2014), and moderate mitral and trivial tricuspid regurgitation.

The patient reported NYHA Class II symptoms and good quality of life over the past 2 years, although he was unable to complete a round of golf without the aid of a golf cart. He was admitted to hospital for HF due to poorly controlled hypertension and volume overload while visiting relatives in the fall of 2015. His vital signs were stable, with a BP of 130/80 mmHg and HR of 62 beats/min, and there was no evidence of volume overload.

The decision was made to switch the patient's ACE inhibitor to sacubitril/valsartan rather than attempt to add spironolactone due to his high-normal potassium level in combination with reduced eGFR and continued periodic intake of NSAIDs. He tolerated the medication change without any other intervention to control potassium and his dose was increased 4 weeks later. At last follow up, his systolic BP had improved, his NT-pro BNP had fallen from 1499 pg/mL to 1103 pg/mL, and he no longer used his golf cart to complete golf activities. Laboratory results are shown in Table 2.

In this case, three important points may be identified:

1. Many patients with HFrEF remain at risk for adverse events despite apparently well-controlled symptoms.[7] Indeed, a great number of these patients will not report symptoms unless pressed for specific information regarding their activities and capabilities. Our patient had initially reported a good quality of life but nevertheless had ongoing

Table 2: Case 2 – Laboratory results

Dates	17-Mar-14	24-Mar-14	30-Mar-16	7-May-16	7-Jun-16	12-Sep-16
Medications	Perindopril 8 mg Furosemide 40 mg qd	Perindopril 8 mg Spironolactone 12.5 mg qd Furosemide 40 mg qd	Perindopril 8 mg Furosemide 40 mg qd	Sacubitril/valsartan 24/26 mg Furosemide 40 mg qd	Sacubitril/valsartan 49/51 mg Furosemide 40 mg qd	Sacubitril/valsartan 97/103 mg Furosemide 40 mg qd
Serum creatinine (µmol/L)	172	190	166	160	172	160
Serum potassium (µmol/L)	4.6	5.8	4.8	4.7	4.6	4.9
BP (mmHg)	116/84	120/80	130/80	124/76	120/76	118/74
NT-proBNP (pg/mL)	5644	–	1499	–	–	1103

limitations to activity associated with daily living. Also, he had been hospitalized and his NT-pro-BNP level remained elevated on HF therapy.

2. While both sacubitril/valsartan and ACE inhibitor therapy may increase serum potassium and creatinine as well as lower systolic BP, there are important differences between the 2 therapies. In the PARADIGM HF trial, sacubitril/valsartan was associated with lower incidence of both hyperkalemia and worsening renal function[6] despite a greater reduction in systolic BP. Indeed, there was no worsening of renal function or serum potassium with switching from the ACE to sacubitril/valsartan and the target dose was reached successfully.

3. Current Canadian Cardiovascular Society (CCS) practice guidelines for the treatment of HFrEF recommend therapy with an ACE inhibitor, a mineralocorticoid receptor antagonist (MRA), and a beta-blocker.[21] The latest guidelines also recommend switching the ACE inhibitor to sacubitril/valsartan whenever possible.[5-7] In the PARADIGM-HF trial, the relative benefit of sacubitril/valsartan over ACE inhibition was present irrespective of baseline MRA use.[6,22] Randomized trials have not given guidance as to which should be introduced first. The CCS's *Heart Failure Companion*, published in 2015, suggests that the order of titration of medications for HF should be individualized according to patient factors.[23] In our case, the patient had a previous history of high-normal potassium and multiple risk factors for hyperkalemia with the addition of spironolactone, so the team elected to switch to sacubitril/valsartan with the intention of rechallenging with MRA in the future, and favourable results were obtained.

Case 3

A 59-year-old male followed in the HF clinic was assessed during a routine visit. He had NYHA I–II symptoms. There was also a history of diabetes and myocardial infarction with previous coronary stenting procedures. His medications were ramipril 5 mg once daily, furosemide 40 mg daily, and as two oral hypoglycemic agents. The patient's eGFR was 40 mL/min/1.73 m^2 and NT-proBNP was 2580 pg/mL. LVEF by radionuclide ventriculography was 48%. He heard about sacubitril/valsartan and questioned whether he was a candidate for this new agent. Sacubitril/valsartan was not prescribed to this patient.

In this last case, the following point is worthwhile of mention: this patient had HF with mid-range ejection fraction (HFmEF).[24] Although systolic

function was impaired, the fact that his LVEF was over 40% would indicate that he would have been excluded from the PARADIGM study and, as such, the benefit of sacubitril/valsartan was unclear. It is noteworthy that in patients with HF and reduced LVEF who were enrolled in PARADIGM-HF, LVEF was a significant and independent predictor of all outcomes.[6] Importantly, sacubitril/valsartan was effective at reducing CV death and HF hospitalization throughout the LVEF spectrum.[25] The role of sacubitril/valsartan in the management of HF and preserved ejection fraction (HFpEF) is currently under evaluation in the Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) study.[26]

Key Points in Optimal Use of Sacubitril/Valsartan

As a matter of guidance in the use of sacubitril/valsartan according to the American Heart Association's Get With The Guidelines® – HF professional educational program and Canadian product monograph,[27,28] physicians should know:

- The starting dose for sacubitril/valsartan is 49/51 mg twice daily, unless the patient is taking lower than guideline-recommended doses of ACEi or ARB prior to initiation of sacubitril/valsartan or has risk factors for hypotension (including patients aged ≥75 years and those with low systolic BP); these latter patients may be started on 24/26 mg twice daily
- The target dose is 97/103 mg twice daily
- After 2-4 weeks, uptitrate to the next dose with the ultimate objective of achieving the target dose
- Monitor systolic BP, renal function, and potassium levels, similar to ACE inhibitor or ARB therapy
- If required, consider allowing time between dosing of sacubitril/valsartan and other vasoactive therapies
- Reassess diuretics doses based on volume status

Additional points revealed during clinical study of sacubitril/valsartan in patients with HFrEF bear highlighting. First, the benefit of sacubitril/valsartan over enalapril on clinical outcomes is evident early after randomization.[23] This suggests that there is some degree of urgency to switch from ACE inhibitors to sacubitril/valsartan in appropriate patients. Indeed, in the second case it was therefore appropriate to switch to sacubitril/valsartan before an MRA was prescribed. Second, the PARADIGM-HF trial found that sacubitril/valsartan was equally effective as enalapril regardless of the perceived risk to patients.[29] Third, the age of patients does not seem to matter when it comes to benefit in clinical outcomes with sacubitril/valsartan; elderly patients benefit as much as their younger counterparts.[30]

Conclusion

As the first-in-class ARNi, sacubitril/valsartan represents a promising new treatment for HF patients, supported by robust clinical trial data. Angiotensin receptor/neprilysin inhibition remains a new concept to practicing physicians. Diligent attention to details, including those discussed in this issue of *Cardiology Rounds*, will ensure maximal benefit to the patient's clinical status and quality of life while limiting potential complications.

Dr. Howlett *is a Clinical Professor, Departments of Cardiac Sciences and Medicine, Libin Cardiovascular Institute of Alberta and University of Calgary, Calgary, Alberta.* ***Dr. Ducharme*** *is the Director, Heart Failure Clinic, Montreal Heart Institute, and a Professor of Medicine, University of Montreal, Montreal, Quebec.* ***Dr. Moe*** *is the Director, Heart Failure Program, St. Michael's Hospital, and a Professor, Department of Medicine, University of Toronto, Toronto, Ontario.*

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