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Review of the 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure: Translating Guidelines to Practice

By GORDON MOE, MD, FRCPC, MSc, and HAYTHAM SHARAR, RN (EC)

The 2017 Comprehensive Update of the Canadian Cardiovascular Society Heart Failure Guidelines was published in November 2017. These guidelines include a comprehensive updated guidance on the diagnosis and management of heart failure (HF) including specific topics related to management of HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction, exercise and rehabilitation, implantable devices, and many other areas of management. In this issue of *Cardiology Rounds*, we will highlight the evidence-based recommendations on the novel treatment options in patients with chronic HFrEF, and discuss typical clinical cases that illustrate how to translate these guidelines to clinical practice.

Guideline-directed medical therapy (GDMT) has significantly improved the mortality and morbidity of heart failure patients with reduced (≤40%) ejection fraction (HFrEF); however, the mortality rate remains significant in these patients.[1]

The Canadian Cardiovascular Society (CCS)[2] and other HF guidelines[3,4] recommend that patients with symptomatic HFrEF be treated initially with a combination of an angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) if ACEi intolerant,[5-7] a β-blocker, and a mineralocorticoid receptor antagonist (MRA). Many randomized clinical trials and meta-analyses have shown the benefit of ACEi[8-10] and β-blockers[11-15] in patients with HFrEF. The usefulness of adding MRA to the combination of ACEi (or ARB) and β-blockers was demonstrated by 2 clinical trials and 1 meta-analysis.[16-18] All of these agents should be titrated to target doses or maximum tolerated evidence-based doses.

In patients who are symptomatic (New York Heart Association [NYHA] Class >II) despite this triple therapy at maximum tolerated doses, the 2017 CCS HF management guidelines recommend modifying treatment with the use of 1 or more novel therapies as discussed in this review.

Angiotensin Receptor-Neprilysin Inhibitor (ARNI)

The CCS HF management guidelines recommend the use of a combination of sacubitril, a neprilysin inhibitor, and valsartan, an ARB, if HF symptoms persist in patients treated with the maximal evidence-based doses of the triple therapy:[2]

We recommend that an ARNI be used in place of an ACEi or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease cardiovascular death, HF hospitalizations, and symptoms (Strong Recommendation; High-Quality Evidence).

The combination of sacubitril and valsartan simultaneously enhances the protective action of natriuretic peptides system and suppresses the detrimental effects of the renin angiotensin aldosterone system.[19] The CCS recommendation is made on the basis of high-quality evidence from the Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, in which sacubitril/valsartan was compared to enalapril.[20]

The 8442 participants in PARADIGM-HF were randomized to sacubitril/valsartan (also called Entresto™ or LCZ696) 200 mg twice daily or enalapril 10 mg twice daily after a 6–8-week single blind run-in phase. Inclusion and exclusion criteria of PARADIGM-HF are presented in Table 1.

St. Michael's Hospital
30 Bond St.,
6-040 Donnelly Wing
Toronto, Ont. M5B 1W8

Table 1: PARADIGM-HF inclusion and exclusion criteria[20]

Inclusion

- Age ≥18 years
- NYHA Class II–IV symptoms
- EF ≤40% (amended to ≤35%)
- Plasma BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL
  - If hospitalized for HF within the previous 12 months: BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL
- Stable dose of a β-blocker and an ACEi or ARB equivalent to at least 10 mg of enalapril daily for ≥4 weeks before screening

Exclusion

- Symptomatic hypotension
  - SBP <100 mm Hg at screening or <95 mm Hg at randomization
- eGFR <30 mL/min/1.73 m^2 at screening or at randomization, or >25% decrease in eGFR (amended to 35%) between screening and randomization
- Serum potassium level >5.2 mmol/L at screening or >5.4 mmol/L at randomization
- History of angioedema or unacceptable side effects during receipt of ACEi or ARB

BNP = B-type natriuretic peptide; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; NT-proBNP = N-terminal pro-BNP; NYHA = New York Heart Association; SBP = systolic blood pressure

The primary outcome was a composite of death from cardiovascular (CV) causes or hospitalization for HF. The trial was stopped early after a median follow-up of 27 months due to the overwhelming benefit of sacubitril/valsartan compared with enalapril. The primary outcome occurred in 914 patients (21.8%) in the sacubitril/valsartan group and 1117 patients (26.5%) in 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; $P<0.001$). These patients also experienced decreases in all-cause mortality, CV mortality, HF hospitalization, and symptoms of HF. The sacubitril/valsartan group had a higher proportion of patients with hypotension but a smaller risk of renal impairment, hyperkalemia, and cough than the enalapril group.

Ivabradine

The CCS guidelines also recommend the addition of ivabradine to GDMT.[2]

We recommend that ivabradine be considered in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT, with a resting heart rate >70 bpm [NOTE: the Health Canada-approved Product Monograph specifies ≥77 bpm]*, in sinus rhythm, and a previous HF hospitalization within 12 months, for the prevention of cardiovascular death and HF hospitalization (Strong Recommendation; Moderate-Quality Evidence).*

Table 2: SHIFT inclusion and exclusion criteria[21,22]

Inclusion

- Age ≥18 years
- NYHA Class II–IV symptoms
- Stable clinical condition for ≥4 weeks
- Optimized and unchanged CHF medications and dosages for ≥4 weeks
- Hospital admission for worsening HF within previous 12 months
- Sinus rhythm
- Resting heart rate ≥70 bpm on the 2 consecutive visits before randomization
  - Measured on 12-lead electrocardiogram after at least 5 minutes rest
- LVEF ≤35%
- HF admission within 12 months

Exclusion

- Recent (<2 months) MI or recent or scheduled coronary revascularization
- Severe primary valvular disease or scheduled surgery of valvular heart disease
- Stroke or transient cerebral ischemia within previous 4 weeks
- Active myocarditis
- Congenital heart diseases
- On list for cardiac transplantation
- Cardiac resynchronization therapy started within previous 6 months
- Pacemaker with atrial or ventricular pacing (except biventricular pacing) >40% of the time, or with stimulation threshold at the atrial or ventricular level ≥60 bpm
- Permanent atrial fibrillation or flutter
- Sick sinus syndrome
- Sinoatrial block
- Second and third degree AV block
- History of symptomatic or sustained (≥30 seconds) ventricular arrhythmia unless a cardioverter/defibrillator implanted
- Cardioverter/defibrillator shock within previous 6 months
- Family history or congenital long QT syndrome or treated with selected QT-prolonging products
- Severe or uncontrolled hypertension: SBP >180 mm Hg or DBP >110 mm Hg
- Sitting SBP <85 mm Hg or current symptomatic hypotension
- Known moderate or severe liver disease, severe renal disease, or anemia

AV = atrioventricular; CHF = congestive heart failure; DBP = diastolic blood pressure; MI = myocardial infarction

Ivabradine is a sinus node selective inhibitor of the depolarizing I_f current. The supporting study evidence is from the **S**ystolic **H**eart failure treatment with the $\mathbf{I_f}$ inhibitor ivabradine **T**rial (SHIFT), which evaluated the use of ivabradine 7.5 mg twice daily versus placebo.[21] Of the 6558 participants in SHIFT, 90% were on a β-blocker and 56% were receiving >50% of the target doses. Inclusion and exclusion criteria are shown in Table 2.[21,22] The primary endpoint – a composite of CV death or HF admission – was reduced by 18% with ivabradine; this was driven mainly by hospital admission for worsening HF (26% relative risk reduction). Ivabradine did not reduce all-cause or CV mortality and there were more withdrawals (21% versus 19%) and bradycardia in the ivabradine group (10% versus 2%). Only 1% of patients withdrew from the study due to bradycardia. Visual symptoms specific to ivabradine occurred rarely (3% versus 1% with placebo; $P<0.0001$) and led to withdrawal in 1% of cases.

Case 1

A 56-year-old female followed in the Heart Failure Clinic for a 3-year history of HFrEF learned of the potential benefits of sacubitril/valsartan through social media and additional online research, and asked whether she could be switched. The patient had nonischemic cardiomyopathy with a left-ventricular (LV) EF of 36%. She had minimal symptom of fatigue. Physical examination revealed a blood pressure (BP) of 110/90 mm Hg and heart rate (HR) of 55 bpm. There were no signs of congestion. Laboratory values included serum creatinine of 89 µmol/L, serum sodium of 145 mmol/L and potassium of 4.8 µmol/L. Her medications are ramipril 10 mg daily and carvedilol 25 mg twice daily. Electrocardiogram was normal with an HR of 60 bpm.

Sacubitril/valsartan was prescribed after ramipril was withheld for 36 hours. The starting dose was 48.6/51.4 mg twice daily. At a follow-up appointment 2 weeks later, her BP was 100/85 mm Hg and her HR was 60 bpm. Kidney function and serum potassium did not change substantially. Sacubitril/valsartan was then increased to the full dose of 97.2/102.8 mg twice daily. The patient remained well clinically and biochemically after 1 month.

Discussion of Case 1

As with many HF cases, this is a relatively straightforward case of a patient with a disease profile that was shown in the PARADIGM-HF study to benefit from sacubitril/valsartan. Because her HR was lower than 70 bpm, she was deemed not a candidate for ivabradine.

Case 2

An 85-year-old male diagnosed with HFrEF 5 years ago presented to the Heart Failure Clinic for a scheduled follow-up. He underwent coronary artery bypass graft surgery 10 years ago and percutaneous coronary intervention 2 years ago. The patient currently had NYHA Class II-III symptoms. He underwent implant of an implantable cardioverter defibrillator (ICD) 7 years ago for secondary prevention due to symptomatic ventricular tachycardia. The patient had a history of a single episode of atrial fibrillation in the past 2 years. His most recent left-ventricular (LV) EF by multiple-gated acquisition scan was 35%. On physical examination, BP was 145/89 mm Hg and HR was 73 bpm. Aside from mild ankle edema, there were no other signs of congestion. The laboratory report indicated a serum creatinine of 128 µmol/L, estimated glomerular filtration rate (eGFR) of 46 mL/min/1.73 m^2, serum sodium of 140 mmol/L, potassium of 4.8 mmol/L with N-terminal pro B-type natriuretic peptide (NT-proBNP) of 2390 pg/mL. Electrocardiography demonstrated sinus rhythm at a rate of 75 bpm and left bundle branch block with QRS duration of 130 msec. The patient was turned down in the past for cardiac resynchronization therapy on the basis of a relatively borderline wide QRS and lack of symptoms.

Current medications included bisoprolol 7.5 mg daily, eplerenone 25 mg daily, candesartan 16 mg daily, furosemide 40 mg twice daily, rosuvastatin 5 mg daily, and apixaban 5 mg twice daily.

This patient appeared to be suitable for sacubitril/valsartan and for ivabradine, according to the CCS guidelines. It was elected to start with sacubitril/ valsartan, in part because of the patient's relatively high BP. The starting dose in this case was the intermediate dose 48.6/51.4 mg twice daily because he was already on a relatively high dose of candesartan, which was discontinued.

The patient was seen in 2 weeks for follow-up to assess his clinical status and consider uptitrating his sacubitril/valsartan. He reported improvement of his symptoms and activity tolerance. He was able to walk his dog for a longer distance than before without stopping to "catch my breath." His ankle swelling subsided completely and weight decreased by 1.4 kg. BP declined to 112/78 mm Hg and HR increased to 82 bpm. His laboratory work revealed serum sodium of 132 mmol/L, serum potassium 4.6 mmol/L, creatinine 136 µmol/L, eGFR 40 mL/min/1.73 m^2, and NT-proBNP 1600 pg/mL. He complained of dizziness when changing position from sitting to standing especially after taking his morning medications.

Sacubitril/valsartan was increased to the full dose of 97.2/102.8 mg twice daily with specific instruction on how to monitor for signs and symptoms of overdiuresis and how to avoid situations causing dizzy spills. As the patient was euvolemic, the furosemide was concurrently reduced from 40 mg twice daily to 40 mg daily.

Discussion of Case 2

The above case illustrates a typical patient with HFrEF attending a regular follow-up in the Heart Failure Clinic. The patient remained symptomatic despite being on maximally tolerated doses of triple GDMT. He had mild kidney dysfunction but normal serum potassium level and eGFR >30 mL/min/1.73 m^2. As mentioned earlier, the patient was a good candidate for both novel therapies; however, the decision was made first to switch candesartan to sacubitril/valsartan, in part because of the relatively high BP. We started him on the intermediate dose of sacubitril/valsartan 48.6/51.4 mg twice daily. There is no need to wait 36 hours for a washout period if the switch is from an ARB to sacubitril/ valsartan, but a 36-hour washout period is required when the switch is from an ACEi. We educated the patient about the potential side effects of the medication and possibility of enhanced diuresis. We also informed the patient about the need to repeat blood work in 10-12 days to check kidney function and electrolytes because of the potential risk of worsening kidney function and hyperkalemia. The patient's furosemide dose was reduced to avoid over-diuresis, and we advised him to spread out his morning medications by 1 hour to avoid dizzy spells induced by possible transient symptomatic hypotension. Furthermore, we asked the patient to call the clinic in a few days to update us about his condition such as BP, and body weight. We repeated his kidney function and electrolytes after 2 weeks. Serum creatinine declined to 115 µmol/L, eGFR was up to 48 mL/min/1.73 m^2, and potassium was 4.3 mmol/L. It was therefore believed that the initial deterioration of kidney function was most likely due to enhanced diuresis with the initiation of sacubitril/valsartan on the last visit.

The following practical guidance may be useful in managing patients when switching to ARNI.

- Drug tolerability, side effects and laboratory monitoring with use of ARNI is similar to that of ACEi or ARB, as noted above.
- The PARADIGM-HF trial excluded patients with a serum potassium >5.2 mmol/L, an eGFR <30 mL/min/1.73 m^2, and symptomatic hypotension with a systolic BP of <100 mm Hg.
- When switching from an ACEi to ARNI, a washout period of at least 36 hours is required to decrease the risk of angioedema; however, no washout period is required for conversion of an ARB to ARNI.
- Sacubitril/valsartan is available in 3 doses: 24.3/25.7 mg (50 mg), 48.6/51.4 mg (100 mg), and 97.2/102.8 mg (200 mg).
- Initial dosing and rate of titration depend on pre-existing treatment and co-morbidities and should be individualized; when selecting a dose or titration schedule, consideration should be given to the likelihood of tolerability and, ultimately, successful titration to doses shown to improve important HF outcomes.

Case 3

A 65-year-old female was followed in the Heart Failure Clinic for ischemic cardiomyopathy. There was a history of myocardial infarction (MI) 10 years ago, for which she was treated with percutaneous coronary intervention. Shortly after the event, she developed ventricular fibrillation and received an ICD for secondary prevention. There was also a history of chronic obstructive airway disease and type 2 diabetes mellitus with diabetic nephropathy and mild renal insufficiency. She presented with NYHA Class II symptoms. LVEF was 34% on echocardiography. Her serum creatinine was 183 µmol/L, eGFR 35 mL/min/1.73 m^2, serum sodium 132 mmol/L, potassium 4.9 mmol/L, and NT-proBNP 7800 pg/mL.

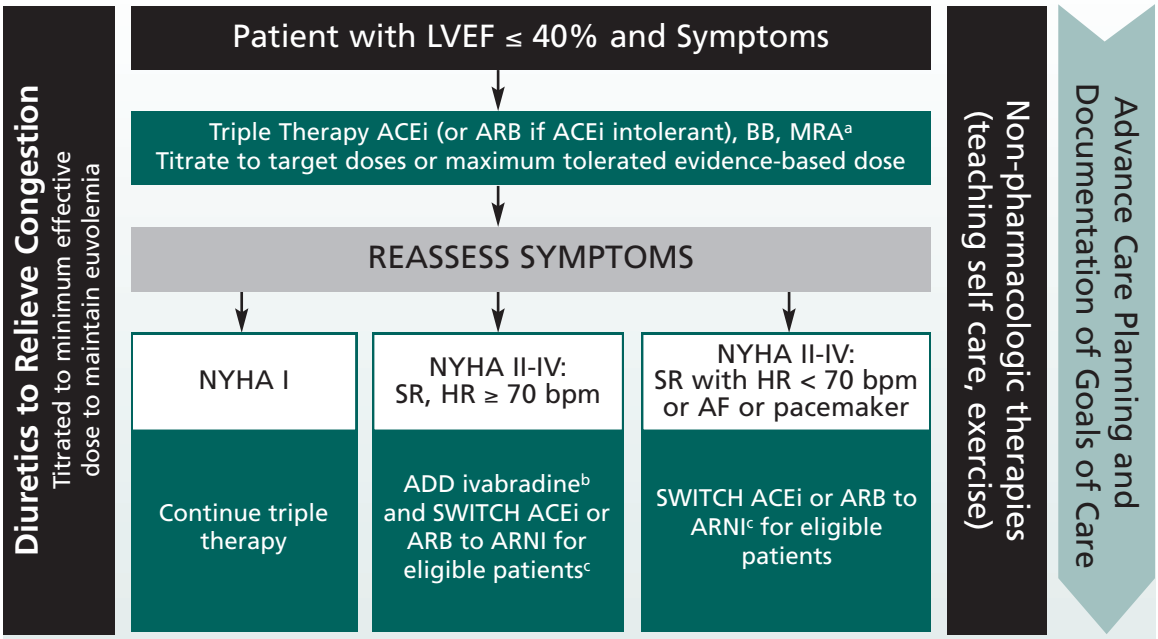
The patient's medications included ramipril 5 mg daily, furosemide 80 mg daily, bisoprolol 10 mg daily, and metformin 1000 mg twice daily. She was intolerant to MRAs due to hyperkalemia. On physical examination, the patient did not appear to be congested. Her BP was 94/60 mm Hg and HR was 69 bpm. Auscultation of the chest revealed overall diminished bronchovesicular sounds; however, there were no crackles or wheezes. Heart sounds were normal. Electrocardiogram demonstrated normal sinus rhythm with HR of 77 bpm and old anterior MI. Holter monitor revealed pacing at 10% of the monitoring period. Average HR was 73 bpm. The patient was believed to be a candidate for ivabradine, which was initiated at 5 mg twice daily.

During follow-up examination 2 weeks later, the patient's BP was 95/50 mm Hg and HR declined to 61 bpm. The dose of ivabradine remained at 5 mg twice daily and the patient remained stable afterward.

Discussion of Case 3

The above case illustrates a patient with a history of HFrEF who is optimized on maximally tolerated GDMT. She developed hyperkalemia with MRA. She was potentially a candidate for novel therapies including ivabradine and sacubitril/valsartan. Her BP was relatively low, but her HR remained above 70 bpm. Her borderline BP and renal dysfunction made this patient less suitable for ARNI. Ivabradine has no effect on BP or kidney function. The above patient

Figure 1: Algorithm for the management of patients with HF and reduced EF[2]



[a] Patients may not need triple therapy with MRA before ARNI or ivabradine initiation. [b] Health Canada-approved indication for ivabradine is in patients with a resting heart rate ≥ 77 bpm. [c] Eligible patients include those with SBP >95 mm Hg and eGFR >30 mL/kg/1.73 m^2.

was on maximum-dose bisoprolol and therefore it was decided to start her on ivabradine 5 mg twice daily. She returned 2 weeks later with no change to her baseline symptoms; HR was down to 56 bpm, BP was 98/53 mm Hg. Repeat blood work demonstrated creatinine of 174 µmol/L, eGFR 37 mL/min/1.73 m^2, serum sodium 137 mmol/L, [patient from ramipril to a low dose of sacubitril/ valsartan 24.3/25.7 mg twice daily. She was advised to stop her ramipril 36 hours before starting the sacubitril/valsartan. The lower HR this time prevented the need to further uptitrate the ivabradine. On the other hand, the improvement on BP with systolic BP >95 mm Hg, stable kidney function, and normal serum potassium level permitted the initiation of sacubitril/valsartan.

Conclusion

Novel therapies including ARNI and ivabradine should be considered for appropriate patients with HFrEF. The PARADIGM-HF study underscores the importance of an early switch to ARNI because of the early benefit demonstrated in mortality and morbidity in the ARNI group soon after randomization.[20] Consideration should be given to individualizing a treatment plan according to the patient's clinical condition, vital signs, and renal function stability. In the first case we were able to switch the patient to the optimal dose of sacubitril/valsartan employing a careful titration strategy and close monitoring of kidney function and symptoms. In the St. Michael's Hospital Heart Failure Clinic, we set up a "Switch Clinic" to enable switching suitable patients to the ARNI combination, to maintain close monitoring of their symptoms, vital signs, and kidney function, and to arrange frequent follow-up appointments within 2-4 weeks until the target dose is reached and optimization is achieved. In the second case, we initially refrained from switching the patient from an ACEi to sacubitril/ valsartan because of low BP and potential risk of hyperkalemia in the context of renal impairment. On the other hand, we decided to start the patient on ivabradine given the fact that the HR remains >70 bpm despite the optimal dose of β-blocker. In the case, the low BP and renal impairment did not significantly affect the decision of starting the ivabradine. The CCS therapeutic algorithm for the management of patients with HFrEF is shown in Figure 1.[2]

Dr. Moe *is a Professor and the Director, Heart Failure Program and Biomarker Laboratory, Cardiology, St. Michael's Hospital, and an Associate Scientist, Li Ka Shing Knowledge Institute, Toronto, Ontario.* ***Mr. Sharar*** *is a full-time Nurse Practitioner – Adult, Heart Failure Clinic, St. Michael's Hospital, Toronto, Ontario.*

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