Original Article

Cost-Effectiveness of Earlier Transition to Angiotensin Receptor Neprilysin Inhibitor in Patients With Heart Failure and Reduced Ejection Fraction

Andrew D.M. Grant, MD,a Derek S. Chew, MD, MSc,a,b Jonathan G. Howlett, MD,a and Robert J.H. Miller, MDa

a Department of Cardiac Sciences, Libin Cardiovascular Institute of Alberta, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
b Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina, USA

ABSTRACT
Background: Angiotensin receptor neprilysin inhibitor (ARNI) therapy improves clinical outcomes in patients with heart failure and reduced left ventricular ejection fraction. However, ARNI therapy uptake remains modest, potentially in part due to perceived cost considerations of early transition from angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy.

Methods: We constructed a decision-analytic Markov model to assess cost-effectiveness of 3 different ARNI initiation strategies according to timing of initiation: (1) de novo, or immediate initiation at baseline, (2) Early or after 3 months, or (3) Late, or after 9 months. Initiation strategies were compared with (4) current care, with utilization of ARNI

Heart failure (HF) represents a major burden on the health care system in developed countries,1 and has been reported to be the single most common cause for hospitalization.2 Over the past few decades, there have been major developments in the treatment of patients with HF with reduced ejection fraction (HFrEF).3 Despite this, rates of admission for HF in Canada have continued to increase, and total costs in 2013 reached almost CAD$500 million.1 The Prospective Comparison of ARNi With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial demonstrated a significant reduction in cardiovascular death and HF hospitalization with combined angiotensin receptor blocker (ARB) and neprilysin inhibitor (ARNi) therapy in patients with HFrEF and persistent symptoms despite conventional medical treatment.1 Based on this trial, guidelines recommend an initial strategy of angiotensin converting enzyme inhibitor (ACEi) or ARB therapy together with beta-blocker (BB) and mineralocorticoid receptor antagonist (MRA) before initiation of ARNi.6-8 Subsequently, the Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-Pro-Bnp in Patients Stabilized From an Acute Heart Failure Episode (PIONEER-HF) trial demonstrated in-hospital initiation of ARNi to be safe, with more than half of patients started on ARNi without prior use of ACEi or ARB, and to be associated with reduced serious adverse events, including HF rehospitalization.9

Despite best efforts in dedicated clinics, patients with HF are often titrated slowly or never reach evidence-based doses of conventional medications.10,11 Failure to achieve early effective medical therapy for HFrEF is associated with excess absolute mortality rates as high as 1% per month that therapy is deferred.12 Less than 20% of stable patients with chronic HFrEF and no contraindication receive ARNi,10 and less than 10% of hospitalized patients are started on therapy.13 This has led to the important question whether earlier transition from ACEi/ARB to ARNi therapy would lead to better patient outcomes.14
derived from a large observational database. Total costs, quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER) were estimated over a 5-year time horizon in the base case analysis.

Results: Current care was associated with the lowest total cost (CAD$26,664) and accrued benefit (3.28 QALYs). The de novo strategy yielded an ICER of $34,727 per QALY gained, whereas Early and Late initiation strategies yielded a less favourable ICER per QALY gained of $35,871 and $40,234, respectively. The model was most sensitive to the cost of ARNi therapy.

Conclusion: A strategy of de novo ARNi initiation is economically attractive and becomes less favourable as the delay of initiation increases. Our results suggest that ARNi therapy should be initiated as soon as possible for patients with heart failure and reduced left ventricular ejection fraction.

To infer the preferred treatment strategy, we evaluated the relative cost-effectiveness of guideline-driven Late initiation, Early initiation, and de novo ARNi initiation compared with current care in the HFrEF population.

Methods

Model design and structure

We constructed a decision-analytic Markov model to address optimal timing of initiating ARNi with sacubitril/valsartan in a simulated cohort of 64-year-old Canadian patients with HFrEF and New York Heart Association functional class II through IV symptoms. Specifically, we performed a cost-utility analysis to project the costs and outcomes of 4 different ARNi initiation strategies: (a) Late initiation, (b) Early initiation, (c) de novo initiation, and (d) current care.

In the Late initiation strategy (a), patients had ACEi/ARB, βB, and MRA therapy introduced and uptitrated over a period of 9 months, with a repeat echocardiogram for left ventricular ejection fraction (LVEF) assessment before being transitioned to ARNi. It was assumed that all patients would be transitioned to ARNi. In the Early initiation strategy (b), medication titration took place over 3 months before all patients being transitioned to ARNi. For the de novo initiation strategy (c), patients were started on ARNi therapy with no preceding trial of ACEi/ARB. The current care strategy (d) was extrapolated from observations in the Change the Management of Patients With Heart Failure (CHAMP-HF) study, a large prospective, observational cohort of adult patients with HFrEF in the United States. Based on this study, after an initial uptake of 14% after a 9-month guideline-recommended medication optimization period, we estimated the average rate of ARNi initiation to be 0.6% per month.

Our Markov model included 3 health states (ie, alive on ARNi, alive on ACEi, and dead) and was designed in TreeAge Pro 2019 (Williamstown, MA). From the perspective of the Canadian public health payer, total costs, life-years, and quality-adjusted life-years (QALYs) were accrued over a monthly cycle-length based on model inputs. For the base case analysis, we chose a 5-year time horizon in light of the limited follow-up duration of the PARADIGM HF trial. To explore the uncertainty in a 5-year time horizon, we also assessed a shorter time horizon (ie, 27 months, the median duration of follow-up in PARADIGM HF) and a 10-year time horizon.

Model inputs

Clinical effectiveness inputs, including rates of all-cause mortality and HF hospitalization, were based on the PARADIGM HF trial (Table 1). The hazard ratios from the PARADIGM HF trial were applied to the cycle-specific all-cause mortality and HF hospitalization rates of patients treated with ACEi to estimate the outcomes associated with ARNi initiation. These rates were then transformed into survival probabilities per 1-month cycle.

Health-related quality of life was directly measured in the PARADIGM HF trial using the European Quality of Life - 5 Dimension, 3 Level questionnaire. The trial-derived utility measures have been previously reported for the enalapril and sacubitril/valsartan treatment groups. We applied a temporary utility decrement for an HF hospitalization event, which approximated a 3-day hospital length of stay, based on prior HF studies that derived utility scores based on a time-trade-off methodology.

Costing inputs included medication costs, diagnostic imaging costs, and downstream costs of HF hospitalizations. Unit costs of enalapril 10 mg and sacubitril/valsartan 97.2/102.8 mg were obtained from reimbursement prices in the Alberta Drug Benefit List. Hospitalization costs were taken from the Canadian Institute for Health Information patient cost estimator. The cost of a transthoracic echocardiogram included both technical and professional fees listed in the
Alberta Schedule of Medical Benefits. Costs were valued in 2018 Canadian dollars. As per contemporary Canadian guidelines for economic evaluations, a 1.5% discount rate was applied to accrued costs and benefits.

### Variability and uncertainty

One-way sensitivity analyses varied a single input parameter at a time using 95% confidence interval bounds and recorded the change in incremental cost per QALY. Variables for which confidence intervals were not available were modelled with wide distributions (± 50%). We also conducted a sensitivity analysis where we excluded the current care strategy; that is, we compared the de novo and Early initiation strategies with the Late initiation strategy, which is the current guideline-recommended approach.

Finally, we conducted a probabilistic sensitivity analysis, where a Monte Carlo simulation of 10,000 iterations was used to propagate the uncertainty in individual model parameters to generate a distribution of expected costs and QALYs. We applied log-normal distributions for all hazard ratios, β-distributions to all probabilities and utilities, and χ-distributions to all costs.

### Results

#### Model validation

To assess model calibration, we estimated the survival probabilities of 2 simulated patient cohorts, one on sacubitril/valsartan and the other on enalapril, and compared the model survival estimations with the PARADIGM HF trial. At 27 months, the median follow-up of PARADIGM HF, the modelled survival was 83.2% and 81.0% for the cohorts on sacubitril/valsartan and enalapril, respectively. These estimated model survival probabilities are similar to those reported in the PARADIGM HF trial: 83.0% (sacubitril/valsartan) and 80.2% (enalapril). In addition, our modelled 5-year and 10-year survival probabilities were 61.5% and 37.8%, respectively. These are similar to 59.1% and 35.4% reported in patients aged 65-74 years in a cohort from the United Kingdom.

#### Model findings

The current care strategy was associated with the lowest total costs ($26,664) and accrued benefit (3.28 QALYs). The Late initiation, Early initiation, and de novo initiation strategies were associated with greater benefit at higher costs (Table 2). Compared with the current care strategy, the de novo initiation strategy yielded an incremental cost of $34,727 per QALY gained. Referencing the current care strategy, the incremental cost-effectiveness ratios (ICERs) for the Late initiation and Early initiation approaches were less favourable at $40,234 and $35,871 per QALY gained, respectively.

Figure 1 displays the relative cost and effectiveness of the different strategies. The Late and Early initiation strategies lie above the "undominated line," indicating reduced cost-effectiveness in comparison with the de novo initiation strategy.

#### Sensitivity analysis

The 1-way sensitivity analyses comparing the de novo initiation strategy with current care are summarized in

---

### Table 1. Base case clinical and costing inputs

| Variable                                      | Base case input | Range          | Distribution | Reference |
|-----------------------------------------------|-----------------|----------------|--------------|-----------|
| **Clinical inputs**                           |                 |                |              |           |
| Rate of HF hospitalization (monthly)          | 0.0487          | 0.040-0.058    | Beta         | McMurray et al. |
| All-cause death rate (monthly)                | 0.0081          | 0.0072-0.0091  | Beta         | McMurray et al. |
| HF hospitalization HR (sacubitril/valsartan vs enalapril) | 0.79           | 0.71-0.89    | Log-normal   | McMurray et al. |
| All-cause death HR (sacubitril/valsartan vs enalapril) | 0.84           | 0.76-0.93    | Log-normal   | McMurray et al. |
| Current care—rate of sacubitril/valsartan uptake per 3 months | 0.019      | 0-0.20        | Beta         | Greene et al. |
| **Utilities**                                 |                 |                |              |           |
| Utility—alive on sacubitril/valsartan         | 0.838           | 0.833-0.843   | Beta         | McMurray et al. and Gaziano et al. |
| Utility—alive on enalapril                    | 0.829           | 0.824-0.834   | Beta         | McMurray et al. and Gaziano et al. |
| Disutility HF hospitalization                 | −0.0066         | −0.0135 to 0  | Beta         | Sandhu et al. and Jagoosild et al. |
| **Costs**                                     |                 |                |              |           |
| HF hospitalization cost                       | $9455           | ± 50%         | Gamma        | Canadian Institute for Health Information |
| Monthly cost of sacubitril/valsartan          | $222.36         | ± 50%         | Gamma        | Government of Alberta |
| Monthly cost of enalapril                     | $15.88          | ± 50%         | Gamma        | Government of Alberta |
| Transthoracic echocardiography                | $250.25         | $125.13-375.38 | Gamma        | Government of Alberta |

All costs are in Canadian dollars. HF, heart failure; HR, hazard ratio.

---

### Table 2. Base case estimates from the Markov cohort model

| Strategy   | Total costs ($) | Total LYs | Total QALYs | ICER* |
|------------|-----------------|-----------|-------------|-------|
| Current    | 26,664          | 3.95      | 3.28        | Reference |
| Late       | 30,751          | 4.04      | 3.38        | $40,234 per QALY gained |
| Early      | 31,299          | 4.07      | 3.41        | $35,871 per QALY gained |
| de novo    | 31,663          | 4.09      | 3.42        | $34,727 per QALY gained |

All costs are in Canadian dollars.

* ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.

---
the Tornado diagram (Fig. 2), and detailed in Supplemental Table S1. The model was most sensitive to the costs of ARNi therapy and hospitalization for HF, as well as the clinical effectiveness of ARNi therapy (ie, hazard ratios for mortality or hospitalization for HF for individuals on ARNi vs ACEi therapy). The input with the greatest effect on the model was the monthly cost of ARNi therapy, which was varied between $111 and $334, resulting in an ICER between $1590 and $67,864 per QALY gained (de novo vs current care). The other input with a substantial influence on the model was the hazard ratio for mortality of ARNi compared with ACEi. When the hazard ratio was varied from 0.76 to 0.93, the ICER ranged between $26,020 and $57,731 per QALY gained (de novo vs current care). When varying the remaining model inputs, the 1-way sensitivity analyses consistently demonstrated an ICER for the de novo initiation strategy consistently below what conventionally would represent good value for money in the Canadian publicly funded health care system.

We conducted a scenario analysis with the Late initiation strategy (ie, the current guideline-recommended approach assuming optimal ARNi uptake) as the reference comparator (Table 3). In this analysis, earlier strategies of ARNi initiation were more economically attractive favouring the Early initiation strategy.

We also explored the impact of several different time horizons, as shown in Table 4. Regardless of the time horizon,
De novo initiation strategy remained the most cost-effective initiation strategy compared with current care.

Discussion

Similar to previous reports in multiple health systems, we found ARNi therapy to be cost-effective compared with ACEi within the context of the Canadian health system. Initiation of ARNi therapy with Late, Early, or de novo initiation strategies was below established WTP thresholds compared with current care. In addition, the de novo initiation strategy was associated with the most favourable ICER. The ICER of the de novo initiation strategy was most sensitive to the monthly cost of ARNi, suggesting that the strategy would also be cost-effective in other health systems with similar drug costs. Overall, our results support earlier initiation of ARNi therapy including the possibility of a de novo initiation strategy.

Previous reports have suggested that ARNi may be economically attractive compared with ACEi therapy in patients with HFREF, with ICERs ranging from approximately $20,000 to $58,000 per QALY gained in the US and European settings. However, these analyses do not deal with the optimal timing of initiating ARNi therapy. Guidelines would suggest that a period of stabilization on ACEi or ARB in addition to βB and MRA be employed before consideration of transition. These recommendations are based on the design of the PARADIGM HF trial and allow for patients to respond to less expensive therapies with improved symptoms and EF, such that ARNi therapy would not be required. Unfortunately, over 75% of patients treated in this way will not have sufficient improvement to avoid an eventual indication for ARNi. This raises important ethical and practical questions about the optimal upfront pharmacologic strategy in this population. Although an initial strategy of standard therapy may be sufficient in a minority of cases, for many patients, this approach may result in a window period of risk, resulting in potentially avoidable rehospitalization or death.

We demonstrate that earlier ARNI initiation strategies have good cost-effectiveness based on ICERs. Although the most appropriate WTP threshold in Canada is not completely established, it is generally agreed that interventions with an ICER below $50,000 are considered cost-effective. All of the ICERs in our study are well below this threshold when considering costs within the context of the Canadian health care system. In particular, a de novo initiation strategy was shown to be the most economically attractive in comparison with current care in our base case analysis. The difference between de novo initiation and either Early or Late initiation was modest, yet our results suggest an economic and clinical benefit to earlier ARNi initiation. When modelled over longer time horizons, the value proposition of the de novo strategy was more substantial. De novo use of ARNi has previously been shown to be safe and represents a simpler strategy with fewer medication dose adjustments. This strategy could potentially increase the proportion of patients receiving ARNi therapy and allow patients to reach optimal medical therapy more quickly.

Notably, the ICER of the de novo initiation strategy was most sensitive to the monthly cost of ARNi. As a result, the generalizability of our results to other health systems is likely to be driven by the comparability of ARNi drug costs. Understanding how these costs will compare with those of other standard and emerging treatments is critically important in a single-payer health care system. This is particularly true in light of other major developments in pharmacologic management of HFREF such as sinus node inhibition, sodium-glucose cotransporter 2 inhibitor therapy, and most recently the soluble guanylate cyclase stimulator vericiguat. Reduction in the price of ARNi would further improve the relative cost-effectiveness from a health care system perspective, with the potential to positively affect the uptake rate of ARNi therapy when offered in a de novo setting.

Limitations

Multiple assumptions are required to model cost-effectiveness. Our analyses did show robust cost effectiveness of the de novo initiation strategy across a range of scenarios.

---

Table 3. Scenario analysis assuming guideline-based ARNi initiation

| Strategy | Total costs ($) | Total QALYs | ICER ($ per QALY gained) |
|----------|----------------|-------------|--------------------------|
| Late     | 30,751         | 4.04        | Reference                |
| Early    | 31,299         | 4.07        | $19,830 per QALY gained  |
| De novo  | 31,663         | 4.09        | $21,520 per QALY gained  |

All costs are in Canadian dollars.

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.

---

Table 4. Scenario analysis exploring different time horizons

| Strategy | Median follow-up (27 mo) | 10-year time horizon |
|----------|--------------------------|----------------------|
|          | Total costs ($)          | Total QALYs | ICER ($ per QALY gained) | Total costs ($) | Total QALYs | ICER ($ per QALY gained) |
| Current care | 13,497             | 1.667        | Reference                | 44,142         | 5.345        | Reference                |
| Late     | 15,134              | 1.691        | 68,755                   | 51,585         | 5.628        | 26,265                   |
| Early    | 15,564              | 1.706        | 53,695                   | 52,297         | 5.673        | 24,819                   |
| De novo  | 15,868              | 1.714        | 50,766                   | 52,744         | 5.697        | 24,426                   |

All costs are in Canadian dollars.

ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.
However, the ICERs estimated by our model were dependent on the clinical effectiveness of ARNi, which was derived from a single large clinical trial. ICERs were also sensitive to the pricing of ARNi therapy. We used the unit pricing from Alberta as sacubitril/valsartan pricing was not uniformly available for all provinces and territories, but among the 5 provinces and 1 territory for which it was publicly available, costing varied by less than 10% overall, and our modelling was carried out over a much larger range.

It was assumed in this study that patients would tolerate ARNi at rates comparable with those enrolled in the PARADIGM HF trial. This is relevant because almost 20% of individuals were unable to complete the run-in phase in PARADIGM HF. This could potentially limit the generalizability of our analysis to real-world populations, although intolerance would influence both costs and associated QALYs in each of the comparator strategies. A large study (Patient Registry Assessing Effectiveness and Safety of Heart Failure Treatment With LCZ696 Across Canada [PARTHENON, ClinicalTrials.gov Identifier: NCT02957409]) to be reported in early 2021 will provide information regarding tolerability from over 1000 Canadian patients. Lastly, we assumed that all patients in the Late and Early initiation strategies would be started on ARNi therapy. Some patients may experience LVEF or symptom improvement before starting ARNi therapy, particularly younger, female patients with new-onset HF. However, previous studies have suggested that there is no heterogeneity in the effectiveness of ARNi therapy across the spectrum of reduced LVEF, potential benefit in patients with borderline reduced LVEF, and preserved benefit in patients with New York Heart Association functional class I or II symptoms. Therefore, ARNi therapy is likely associated with cardiovascular benefit even in patients with improved LVEF or symptoms on ACEi or ARB.

Conclusion
We demonstrated that earlier initiation of ARNi therapy is economically attractive compared with current care. Cost-effectiveness was most favourable with a de novo initiation strategy and became less favourable as initiation delay increased. Our results suggest that ARNi therapy should be initiated as soon as possible for patients with HFrEF.

Funding Sources
D.S.C. is supported by a Canadian Institutes of Health Research Banting Fellowship and an Arthur JE Child Fellowship.

Disclosures
The authors have no conflicts of interest to disclose.

References
1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nature Rev Cardiol 2011;8:30-41.
2. Ross H, Howlett J, Arnold JMO, et al. Treating the right patient at the right time: access to heart failure care. Can J Cardiol 2006;22:749-54.
3. McDonald MA, Ashley EA, Fedak PWM, et al. Mind the gap: current challenges and future state of heart failure care. Can J Cardiol 2017;33:1434-49.
4. Tran DT, Ohinmaa A, Thanh NX, et al. The current and future financial burden of hospital admissions for heart failure in Canada: a cost analysis. CMAJ Open 2016;4:365-70.
5. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:777-803.

7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129-200.

8. Ezekowitz JA, O’Meara E, McDonald MA, et al. 2017 Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol 2017;33:1342-433.

9. Morrow DA, Velazquez EJ, Devore AD, et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF Trial. Circulation 2019;139:2285-8.

10. Greene SJ, Fonarow GC, DeVore AD, et al. Longitudinal titration of medical therapy for heart failure with reduced ejection fraction: CHAMP-HF registry. J Am Coll Cardiol 2019;73:2365-83.

11. DeFilippis EM, Butler J, Vaduganathan M. Waiting period before implantable cardioverter-defibrillator implantation in newly diagnosed heart failure with reduced ejection fraction: a window of opportunity. Circ Heart Fail 2017;10:1-4.

12. Zaman S, Zaman SS, Scholtes T, et al. The mortality risk of deferring optimal medical therapy in heart failure: a systematic comparison against norms for surgical consent and patient information leaflets. Eur J Heart Fail 2017;19:1401-9.

13. Luo N, Lippmann SJ, Mentz RJ, et al. Relationship between hospital characteristics and early adoption of angiotensin-receptor/neprilysin inhibitor among eligible patients hospitalized for heart failure. J Am Heart Ass 2019;8:e010484.

14. Gracia E, Hamid A, Butler J. Timely management of new-onset heart failure. Circulation 2019;140:621-3.

15. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. JAMA Cardiol 2016;1:666-72.

16. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-effectiveness of sacubitril-valsartan in patients with heart failure with reduced ejection fraction. Ann Int Med 2016;165:681-9.

17. Government of Alberta. Alberta Drug Benefit List. Available at: https://idb.ab.bluecross.ca/idb/lead.do. Accessed December 8, 2019.

18. Canadian Institute for Health Information. Patient Cost Estimator. Available at: https://www.cihi.ca/en/patient-cost-estimator. Accessed December 10, 2019.

19. Government of Alberta. Schedule of Medical Benefits. Available at: https://open.alberta.ca/publications/somb-2019-10-01. Accessed December 8, 2019.

20. Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Health Technologies: Canada. 4th ed. Ottawa, Ontario: The Agency, 2017.

21. Taylor CJ, Ordóñez-Mena JM, Roalf AK, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. BMJ 2019;364:k223.

22. McMurray JJV, Trueman D, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart 2018;104:1006-13.

23. King JB, Shah RU, Bress AP, Nelson RE, Bellows BK. Cost-effectiveness of sacubitril-valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. JACC Heart Fail 2016;4:392-402.

24. Ademi Z, Pféil AM, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. Swiss Med Week 2017;147:1-25.

25. van der Pol S, Degener F, Postma MJ, Vemer P. An economic evaluation of sacubitril/valsartan for heart failure patients in the Netherlands. Value Health 2017;20:388-96.

26. Rocchi A, Menon D, Verma S, Miller E. The role of economic evidence in Canadian oncology reimbursement decision-making: to lambda and beyond. Value Health 2008;11:771-83.

27. Savarese G, Vedin O, D’Amario D, et al. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. JACC Heart Fail 2019;7:306-17.

28. Vallejo-Torres L, García-Lorenzo B, Castillo I, et al. On the estimation of the cost-effectiveness threshold: why, what, how? Value Health 2016;19:558-66.

29. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010;376:875-85.

30. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

31. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883-93.

32. Ghimire A, Fine N, Ezekowitz JA, et al. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study. Eur Heart J 2019;40:2110-7.

33. Chew DS, Heikdi H, Schmidt G, et al. Change in left ventricular ejection fraction following first myocardial infarction and outcome. JACC Clin Electrophysiol 2018;4:672-82.

34. Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction: the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure. Circ Heart Fail 2016;9:e002744.

35. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-20.

36. Jaagold P, Dawson NV, Thomas C, et al. Outcomes of acute exacerbation of severe congestive heart failure: quality of life, resource use, and survival. SUPPORT Investigators. The Study to Understand Prognosis and Preferences for Outcomes and Risks of Treatments. Arch Intern Med 1998;158:1081-9.

Supplementary Material

To access the supplementary material accompanying this article, visit CJC Open at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.05.009.