



Original Article

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

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## 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

## RÉSUMÉ

**Contexte :** Le traitement par un antagoniste des récepteurs de l'angiotensine/inhibiteur de la néprilysine (ARNi) améliore les résultats cliniques chez les patients présentant une insuffisance cardiaque et une fraction d'éjection ventriculaire gauche réduite. L'adoption d'un tel traitement demeure toutefois modeste, peut-être en partie à cause des perceptions quant au coût associé à la substitution précoce d'un inhibiteur de l'enzyme de conversion de l'angiotensine ou d'un antagoniste des récepteurs de l'angiotensine.

**Méthodologie :** Nous avons mis au point un modèle de Markov appliqué à l'analyse décisionnelle afin d'évaluer le rapport coût-efficacité de trois stratégies d'instauration d'un traitement par un

Heart failure (HF) represents a major burden on the health care system in developed countries,<sup>1</sup> and has been reported to be the single most common cause for hospitalization.<sup>2</sup> Over the past few decades, there have been major developments in the treatment of patients with HF with reduced ejection fraction (HFrEF).<sup>3</sup> Despite this, rates of admission for HF in Canada have continued to increase, and total costs in 2013 reached almost CAD\$500 million.<sup>4</sup> 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.<sup>5</sup> Based on this trial, guidelines recommend an initial strategy of angiotensin converting enzyme inhibitor (ACEi) or ARB therapy together with beta-blocker ( $\beta$ B) and mineralocorticoid receptor antagonist (MRA) before initiation of ARNi.<sup>6-8</sup> 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.<sup>9</sup>

Despite best efforts in dedicated clinics, patients with HF are often titrated slowly or never reach evidence-based doses of conventional medications.<sup>10,11</sup> 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.<sup>12</sup> Less than 20% of stable patients with chronic HFrEF and no contraindication receive ARNi,<sup>10</sup> and less than 10% of hospitalized patients are started on therapy.<sup>13</sup> This has led to the important question whether earlier transition from ACEi/ARB to ARNi therapy would lead to better patient outcomes.<sup>14</sup>

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**Ethics Statement:** The research reported in this paper adhered to relevant ethical guidelines.

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See page 452 for disclosure information.

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,  $\beta$ B, 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.<sup>10</sup> 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.<sup>10</sup>

Our Markov model included 3 health states (ie, alive on ARNi, alive on ACEi, and dead) and was designed in TreeAge

ARNi, selon le moment de la mise en route : 1) instauration *de novo*, c'est-à-dire instauration immédiate dès le départ; 2) instauration précoce (après trois mois); ou 3) instauration tardive (après neuf mois). Les stratégies d'instauration ont été comparées à 4) la norme de soins actuelle, l'utilisation des ARNi étant dérivée d'une importante base de données observationnelles. Dans l'analyse du scénario de référence, les coûts totaux, les années de vie pondérées par la qualité (QALY pour *quality-adjusted life-years*) et le rapport coût-efficacité différentiel (RCED) ont été estimés sur une période de cinq ans.

**Résultats :** La norme de soins actuelle était associée au coût le plus faible (26 664 \$CAD) et à un bienfait cumulé (3,28 QALY). La stratégie *de novo* a donné lieu à un RCED de 34 727 \$ par QALY gagnée, tandis que les RCED des stratégies d'instauration précoce et tardive étaient moins favorables et s'établissaient respectivement à 35 871 \$ et à 40 234 \$. Le modèle s'est révélé plus sensible au coût du traitement par un ARNi.

**Conclusion :** La mise en route d'un traitement par un ARNi *de novo* est attrayante sur le plan financier, et devient de moins en moins intéressante à mesure que le temps passe. Nos résultats indiquent qu'il faudrait instaurer le traitement par un ARNi le plus rapidement possible chez les patients présentant une insuffisance cardiaque et une fraction d'éjection ventriculaire gauche réduite.

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<sup>5</sup> (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.<sup>15</sup> 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.<sup>16</sup>

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.<sup>17</sup> Hospitalization costs were taken from the Canadian Institute for Health Information patient cost estimator.<sup>18</sup> The cost of a transthoracic echocardiogram included both technical and professional fees listed in the

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

Variable	Base case input	Range	Distribution	Reference
<b>Clinical inputs</b>				
Rate of HF hospitalization (monthly)	0.0487	0.040-0.058	Beta	McMurray et al. <sup>5</sup>
All-cause death rate (monthly)	0.0081	0.0072-0.0091	Beta	McMurray et al. <sup>5</sup>
HF hospitalization HR (sacubitril/valsartan vs enalapril)	0.79	0.71-0.89	Log-normal	McMurray et al. <sup>5</sup>
All-cause death HR (sacubitril/valsartan vs enalapril)	0.84	0.76-0.93	Log-normal	McMurray et al. <sup>5</sup>
Current care—rate of sacubitril/valsartan uptake per 3 months	0.019	0-0.20	Beta	Greene et al. <sup>10</sup>
<b>Utilities</b>				
Utility—alive on sacubitril/valsartan	0.838	0.833-0.843	Beta	McMurray et al. <sup>5</sup> and Gaziano et al. <sup>15</sup>
Utility—alive on enalapril	0.829	0.824-0.834	Beta	McMurray et al. <sup>5</sup> and Gaziano et al. <sup>15</sup>
Disutility HF hospitalization	-0.0066	-0.0135 to 0	Beta	Sandhu et al. <sup>16</sup> and Jaagosild et al. <sup>36</sup>
<b>Costs</b>				
HF hospitalization cost	\$9455	± 50%	Gamma	Canadian Institute for Health Information <sup>18</sup>
Monthly cost of sacubitril/valsartan	\$222.36	± 50%	Gamma	Government of Alberta <sup>17</sup>
Monthly cost of enalapril	\$15.88	± 50%	Gamma	Government of Alberta <sup>17</sup>
Transthoracic echocardiography	\$250.25	\$125.13-375.38	Gamma	Government of Alberta <sup>19</sup>

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

Alberta Schedule of Medical Benefits.<sup>19</sup> 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.<sup>20</sup>

**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 γ-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).<sup>5</sup> 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.<sup>21</sup>

**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.

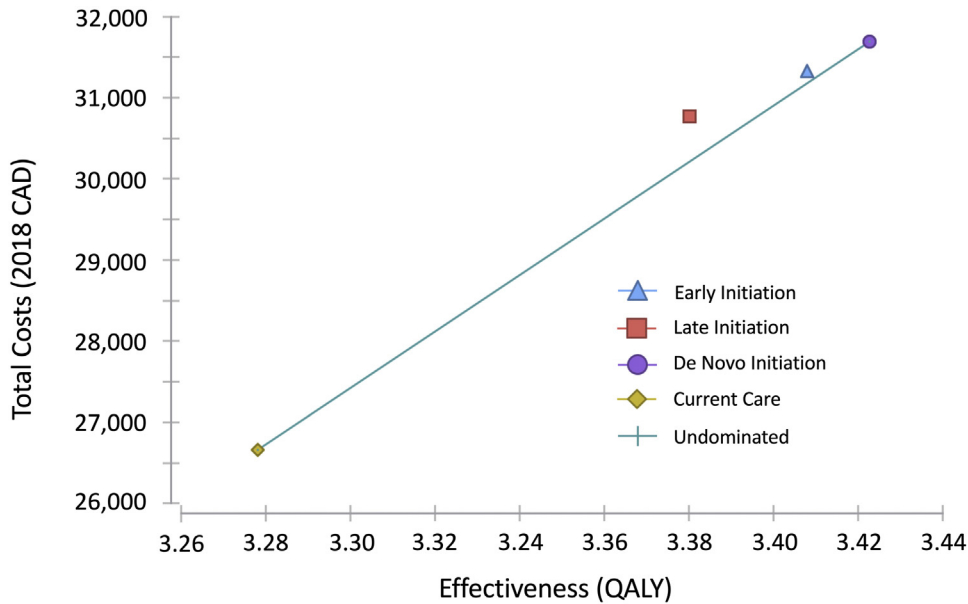
**Sensitivity analysis**

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

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

Strategy	Total costs (\$)	Total LYs	Total QALYs	ICER*
Current care	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
<i>De novo</i>	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.  
\*ICER calculations may not reflect the ratio of reported incremental costs and QALYs due to differences in rounding.



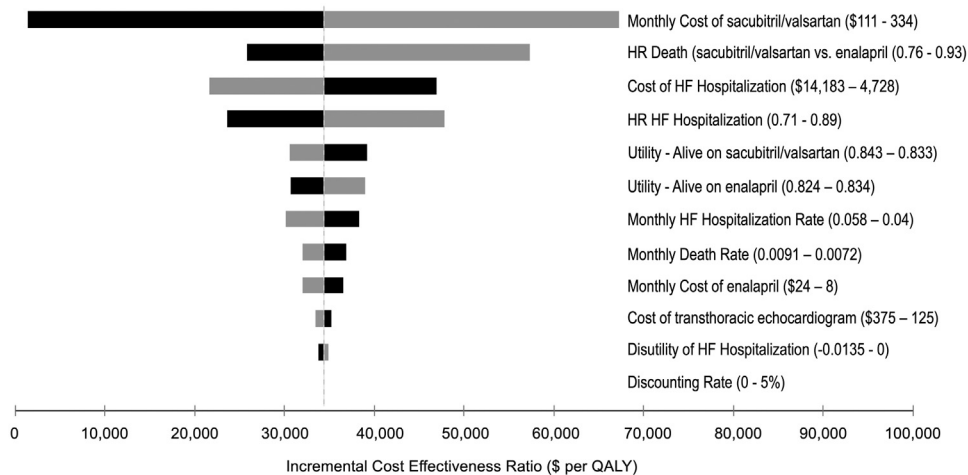
**Figure 1.** Cost-effectiveness plane showing the base case total costs and total quality-adjusted life-years (QALYs) for each strategy. All costs are in Canadian dollars (CAD).

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,



**Figure 2.** Tornado diagram summarizing 1-way sensitivity analyses on the incremental cost-effectiveness ratio (cost per QALYs gained). Grey and black bars denote the effects of the upper and lower bounds of each variable input, respectively. That is, the upper bound may have differential effects on the incremental cost-effectiveness ratio depending on the variable input. All costs are in Canadian dollars. HF, heart failure; HR, hazard ratio; QALY, quality-adjusted life-year.

**Table 3. Scenario analysis assuming guideline-based ARNi initiation**

Strategy	Total costs (\$)	Total LYs	Total QALYs	ICER*
Late	30,751	4.04	3.38	Reference
Early	31,299	4.07	3.41	\$19,830 per QALY gained
<i>De novo</i>	31,663	4.09	3.42	\$21,520 per QALY gained

All costs are in Canadian dollars.  
 ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.  
 \*ICER calculations may not reflect the ratio of reported incremental costs and QALYs due to differences in rounding.

the *de novo* initiation strategy remained the most cost-effective initiation strategy compared with current care.

Figure 3 shows the cost-effectiveness acceptability curve, which shows the probability of each strategy having the best net health benefit at different willingness-to-pay (WTP) thresholds. At all thresholds, the Late and Early initiation strategies were not considered to be economically attractive. At a threshold of \$50,000 per QALY gained, the *de novo* strategy was the most cost-effective strategy in 73% of simulations.

**Discussion**

Similar to previous reports in multiple health systems,<sup>15,16,22-25</sup> 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.<sup>26</sup> 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 \$29,000 to \$58,000 per QALY gained in the US and European settings.<sup>15,16,22-25</sup> 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  $\beta$ B and MRA be employed before consideration of transition.<sup>6-8</sup> 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.<sup>27</sup> 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.<sup>26,28</sup> 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<sup>9</sup> 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,<sup>29</sup> sodium-glucose cotransporter 2 inhibitor therapy,<sup>30</sup> and most recently the soluble guanylate cyclase stimulator vericiguat.<sup>31</sup> 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**

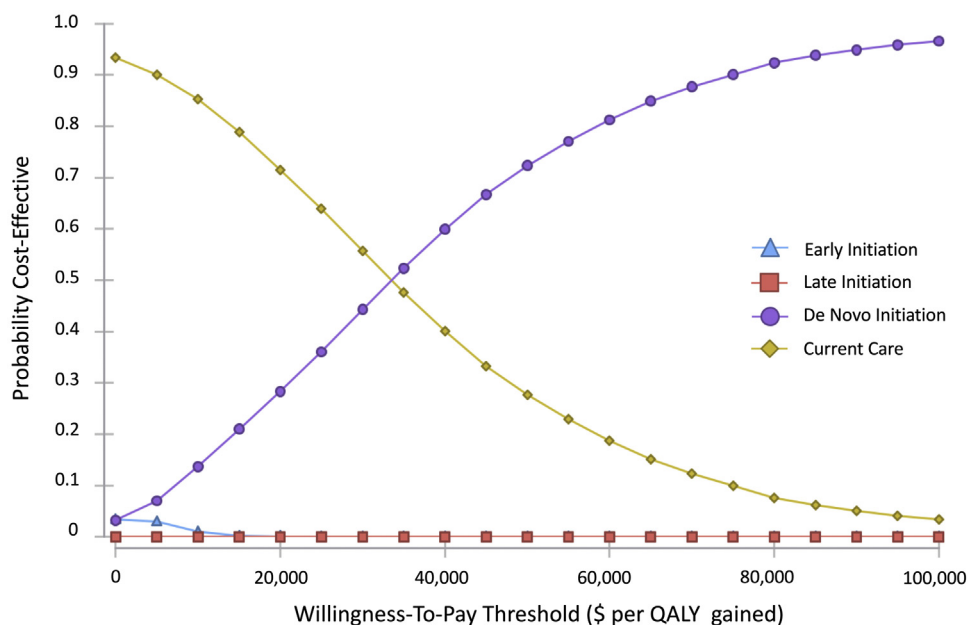
Multiple assumptions are required to model cost-effectiveness. Our analyses did show robust cost effectiveness of the *de novo* initiation strategy across a range of scenarios.

**Table 4. Scenario analysis exploring different time horizons**

Strategy	Median trial 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
<i>De novo</i>	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.





**Figure 3.** Cost-effectiveness acceptability curve showing the probability of a strategy being cost-effective over a range of willingness-to-pay thresholds. All costs are in Canadian dollars. 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.<sup>5</sup> 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](https://clinicaltrials.gov/ct2/show/study/NCT02957409) 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.<sup>32,33</sup> However, previous studies have suggested that there is no heterogeneity in the effectiveness of ARNi therapy across the spectrum of reduced LVEF,<sup>34</sup> potential benefit in patients with borderline reduced LVEF,<sup>35</sup> and preserved benefit in patients with New York Heart Association functional class I or II symptoms.<sup>5</sup> 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.

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## Disclosures

The authors have no conflicts of interest to disclose.

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### Supplementary Material

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