Optimal Usage of Sacubitril/Valsartan for the Treatment of Heart Failure: The Importance of Optimizing Heart Failure Care in Canada

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ABSTRACT

Background: Heart failure (HF) with reduced ejection fraction represents approximately 50% of the 600,000 Canadians currently living with HF and over 90,000 new cases diagnosed each year. The angiotensin receptor neprilysin inhibitor, sacubitril/valsartan, demonstrated superior efficacy in reducing cardiovascular death and HF hospitalization over standard of care therapy.

Methods: The potential magnitude of benefit in Canada with respect to preventing or postponing deaths and reducing hospitalizations resulting from its optimal implementation in patients with HF with an ejection fraction <40% was estimated based on published sources.

More than 600,000 Canadians are currently living with heart failure (HF), and over 90,000 new cases are diagnosed each year in Canada.1 HF with reduced ejection fraction (HFrEF) represents approximately 50% of these patients.2 There is robust clinical evidence for efficacious, guideline-directed therapies in HFrEF.3 However, despite wide recognition of these therapies, the rate of clinical uptake remains variable and HF continues to be characterized by high mortality rates, frequent hospitalizations, and high rates of readmission after hospital discharge.2,4-7 At present, up to 50% of patients with HF will die within 5 years of diagnosis, accounting for approximately 22,000 deaths annually in Canada.8-11

The angiotensin receptor neprilysin inhibitor (ARNI), sacubitril/valsartan, has demonstrated superior efficacy in reducing cardiovascular (CV) death and HF hospitalization compared with enalapril in the Prospective Comparison of

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Results: Of the potentially eligible 225,562 patients, this would amount to the prevention of 4699 cardiovascular deaths and first HF hospitalizations, 3698 thirty-day HF readmissions, and 2820 deaths due to all-cause mortality. The number of patients receiving sacubitril/valsartan nationally in 2018 was 27,267. This represents approximately 12% of the calculated eligible population for this therapy in Canada.

Conclusions: The findings from this analysis suggest that a substantial number of deaths, hospitalizations, and HF readmissions could potentially be avoided by optimal usage of sacubitril/valsartan therapy in Canada. This emphasizes the importance of rapidly and appropriately implementing evidence-based medications into routine clinical practice, to achieve the best possible outcomes for our patients with HF and to reduce the high burden and cost of HF in Canada.

ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. This is an important medication given the magnitude of benefit seen over and above current standard of care. Sacubitril/valsartan was approved by Health Canada in October 2015 for the treatment of HFrEF in patients with New York Heart Association class II or III symptoms. It is expected, as with all new drugs, that there will be a delay from approval to appropriate implementation in the clinical setting. Despite decades of guideline recommendations for angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers, there is still a significant treatment gap with many studies including those representing Canadian data, reporting less than 70% of eligible patients being initiated on these medications and less than 30% of patients achieving target doses. A recent registry, CHAMP-HF, which included over 3500 patients, also showed low numbers for ARNI prescription in eligible patients with HF with only 14% receiving target doses.

A US-based study by Fonarow et al. suggested that with optimal implementation of sacubitril/valsartan the potential mortality reduction would be in the range of 18,230-41,017 persons, assuming an eligible HF population of approximately 2.3 million. Although the absolute difference in number of lives saved would be smaller, the relative difference in lives saved in the HF population in Canada is expected to be similar. Given that HF is the second leading cause of hospitalization in Canada for patients older than 65 years, hospitalizations and postdischarge readmissions are a significant public health issue, with readmission rates ranging from 20% to 50% at 30 days after discharge and up to 59% at 1 year after discharge. The direct costs of treating HF alone in 2012 were estimated at CAD$2.89 billion per year, approximately 1% of Canada’s GDP. The objective of this analysis is to describe the potential magnitude of benefit with respect to preventing or postponing deaths and reducing hospitalizations resulting from optimal implementation of sacubitril/valsartan in patients with HF with an ejection fraction <40% in Canada.

Methods
Potential patient eligibility for sacubitril/valsartan therapy was established based on the indication approved by Health Canada and following the methods applied in a previous study completed in the United States. The eligible population, Canadian and per province, was used from 2018 Statistics Canada data for adults over 40 years of age. Prevalence data from the Canadian Chronic Disease Surveillance System were used to calculate the prevalence of HF. The Canadian Chronic Disease Surveillance System is a network of provincial and territorial surveillance systems that collaborate to link health insurance registry databases and is supported by the Public Health Agency of Canada. The most recent available prevalence data were for 2015 (2014 for Saskatchewan), and were applied to the 2018 populations. Assumptions were made based on similar exclusions used by Fonarow et al. to define the appropriate disease and treatment population. Rates of possible contraindications, medical exceptions, intolerance, and other relevant reasons for not applying ACEI/angiotensin receptor blocker (ARB)/ARNI therapy were derived from published sources and applied to the Canadian population described above.

The proportion of HF patients with HFrEF is 56%, and the proportion of patients with NYHA class II or III symptoms ranged from 64% to 75%. We decided to use a prevalence of 70% for NYHA class II or III symptoms based on estimates from the current published literature. To exclude patients who would be ineligible for sacubitril/valsartan therapy, 5% of patients were removed to account for patients receiving comfort care and those requiring advanced therapies (inotropic therapy, mechanical assist devices, or heart transplant). To account for intolerance expected with ACEI, 7% of patients were removed and finally, based on the degree of adverse events reported from the
sacubitril/valsartan run-in period from the PARADIGM-HF study. 6.4% of the calculated estimated population was removed as ineligible for therapy.6,12

The magnitude of event reduction for ARNI therapy was determined from the PARADIGM-HF trial.12 The number needed to treat (NNT) to avoid 1 event, as well as a dosage assumption specific to Novartis Pharmaceuticals Canada Inc. Adherence assumptions were based on outcomes in PARADIGM-HF, standardized to 12 months.

According to CCDSS data, the prevalence for Saskatchewan was not available for 2015; therefore, the 2014 prevalence was used for provincial population calculations. The 2014 prevalence was not included in consideration of the overall Canadian prevalence. Prevalence data for the territories were not available. NNT calculated based on outcomes in PARADIGM-HF, standardized to 12 months.

CCDSS, Canadian Chronic Disease Surveillance System; CV, cardiovascular; HF, heart failure; NNT, number needed to treat; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

Table 1. Canadian heart failure population and projected outcome data for patients optimally treated with sacubitril/valsartan therapy

|                | Canada | QC  | ON  | MB  | SK  | AB  | BC  | NL  | PEI | NS  | NB  |
|----------------|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| HF prevalence  | 3.70%  | 3.68%| 3.59%| 4.28%| 4.58%| 3.43%| 4.14%| 4.51%| 3.40%| 3.35%| 3.50%|
| Eligible pop.  | 225,562| 53,137| 84,080| 8681 | 44,55 | 19,644| 35,180| 4455 | 913  | 5804 | 5000 |
| CV death or 1st HF hospitalization prevented (NNT = 48) | 4699 | 1107 | 1752 | 181 | 165 | 448 | 733 | 93 | 19 | 121 | 104 |
| CV death prevented (NNT = 70) | 3222 | 759 | 1201 | 124 | 113 | 307 | 503 | 64 | 13 | 83 | 71 |
| HF hospitalization prevented (NNT = 80) | 2820 | 664 | 1051 | 109 | 99 | 269 | 440 | 56 | 11 | 73 | 63 |
| All-cause mortality prevented (NNT = 80) | 2820 | 664 | 1051 | 109 | 99 | 269 | 440 | 56 | 11 | 73 | 63 |
| 30-day HF readmission prevented (NNT = 61) | 3698 | 871 | 1378 | 142 | 130 | 352 | 577 | 73 | 15 | 95 | 82 |

Discussions:

The data presented highlight a significant care gap that is potentially modifiable by ensuring the optimal prescription of evidence-based therapy. By administering guideline-directed medical therapy to eligible patients, a significant reduction in HF morbidity and mortality could be achieved. This analysis aims to present this case using sacubitril/valsartan as an example. These issues represent a serious public health concern, and each individual HF patient’s illness trajectory is fraught with inherent risk for future events and has an unpredictable course. The nature of the syndrome necessitates multiple contacts with the healthcare system for acute and maintenance therapy. After index hospitalization for HF, patients who are readmitted within 2 years have a two-and-a-half times increased risk of mortality compared with patients who have no additional hospitalizations.31-33 Each subsequent and additional hospitalization increases a patient’s risk of mortality.34-36 The risk of hospitalization is especially high after an acute event in

Discussion:

The data presented highlight a significant care gap that is potentially modifiable by ensuring the optimal prescription of evidence-based therapy. By administering guideline-directed medical therapy to eligible patients, a significant reduction in HF morbidity and mortality could be achieved. This analysis aims to present this case using sacubitril/valsartan as an example. These issues represent a serious public health concern, and each individual HF patient’s illness trajectory is fraught with inherent risk for future events and has an unpredictable course. The nature of the syndrome necessitates multiple contacts with the healthcare system for acute and maintenance therapy. After index hospitalization for HF, patients who are readmitted within 2 years have a two-and-a-half times increased risk of mortality compared with patients who have no additional hospitalizations.31-33 Each subsequent and additional hospitalization increases a patient’s risk of mortality.34-36 The risk of hospitalization is especially high after an acute event in
the first 30 days, and although a common target of therapy, there has been little improvement in rates of 30-day readmissions before sacubitril/valsartan. Based on the 2016 Report on the Health of Canadians from the Heart and Stroke Foundation, the 30-day readmission rate is 21%. Appropriate use of sacubitril/valsartan therapy in the indicated population could potentially decrease the number of hospital admissions for HF by 2820 (1804-4059) annually and 30-day readmissions by 3698 (2367-5325) in Canada. This measure alone could have a large impact on clinical resource use and health care expenditure, particularly in a publicly funded health care system such as we have in Canada. Frequent hospitalizations are not only costly but are also associated with significantly diminished health-related quality of life for patients. Although the length of inpatient hospital stays is declining for patients with HF, the absolute number of patients admitted to hospital is increasing. This is especially important to note because the elderly HF population uses most of the hospital resources, and Statistics Canada projects a dramatic increase in the octogenarian population as the population demographic shifts. As a palliative condition in this population, maintaining good health-related quality of life and a stable functional status is imperative. HF accounts for approximately 22,000 deaths annually in Canada, which is comparable to the number of deaths from breast, colorectal, and pancreatic cancer combined. This significant impact highlights the need to investigate and employ new treatment strategies to improve on the current HF treatment standards. Based on the findings of this study, if sacubitril/valsartan therapy was used at the optimal rate in Canada, approximately 3222 (2062-4640) deaths could be prevented from CV causes specifically, and this would represent a 15% reduction in the annual rate of HF-associated deaths (3222/22,000). As rates of HF are projected to increase by 25% by 2030, the opportunity for the significant impact remains high.

There is often a delay from approval to wide uptake and prescription of new medications. The safety and efficacy profile of medication is the primary, most important factor affecting prescribing practices. Although the episodes of symptomatic hypotension experienced by patients in the PARADIGM trial were higher in the sacubitril/valsartan group (14%) than the enalapril group (9.2%), the number of patients who needed to discontinue sacubitril/valsartan therapy due to overall adverse events was significantly lower (10.7%) than patients taking enalapril (12.3%). In Canada, we estimated that 12% of patients eligible for therapy with sacubitril/valsartan are being prescribed this life-saving drug. Underutilization of guideline-recommended evidence-based therapies can be attributed to various patient-related, physician-related, and nonmedical factors. Patient-related factors can include comorbidities leading to intolerance or contraindications. Physician-related factors include medical inertia, focus on symptom relief rather than mortality, and fear of adverse events. This is true for all medications, but the number of barriers tend to increase with the degree of polypharmacy. The uptake of sacubitril/valsartan faces unique challenges because before its initiation, standard triple therapy (ACEI, beta-blocker, and mineralocorticoid receptor

| Table 2. Comparison of Canadian patients receiving sacubitril/valsartan and those eligible for therapy based on Novartis Pharmaceutical Inc. estimated data |
|---------------------------------------------------------------|
| CV death or 1st HF hospitalization (NNT = 48) (population 27,267) | 568 (364-818) | 4699 (3007-6767) |
| CV death (NNT = 70) (population 27,267) | 390 (250-562) | 3222 (2062-4640) |
| HF hospitalization (NNT = 80) (population 27,267) | 340 (218-490) | 2820 (1804-4059) |
| All-cause mortality (NNT = 80) (population 27,267) | 340 (218-490) | 2820 (1804-4059) |
| 30-day HF readmission (NNT = 61) (population 27,267) | 447 (286-644) | 3698 (2367-5325) |

CV, cardiovascular; HF, heart failure; NNT, number needed to treat. Provided by Novartis Pharmaceuticals Canada Inc, based in part on information provided by IQVIA Solutions Canada Inc. All rights reserved.
antagonist) needs to be titrated to maximally tolerated doses, which can often take 4–6 months to accomplish. Use of sacubitril/valsartan also requires discontinuation of the current ACEI or ARB therapy and closer initial monitoring, which could be perceived as more challenging. Nonmedical factors can include medication cost and access to health care systems. For patients not covered by provincial or private drug benefit plans, this could be a significant barrier. Patients who remain symptomatic with significant functional impairments or frequent hospitalizations despite first-line therapy should be referred for specialist care, as recommended in the Canadian CV Society guidelines. Wait times for access to specialists or regional HF clinics can vary by region and may impact uptake of sacubitril/valsartan prescription, as specialists are more likely to prescribe newer HF medications than generalists. At present, most patients with HF are cared for by primary care physicians and general internists. The overall cost-effectiveness of ARNI therapy was examined by the CADTH Common Drug Review and estimated to have an incremental cost-utility ratio of $42,787 per quality-adjusted life-year compared with ACEI. This cost has been corroborated in other American studies and also meets the ACC/AHA benchmark of approximately $66,000 per quality-adjusted life-year for acceptable cost-effectiveness ratio and matches other high-value accepted CV interventions. The cost to the Canadian health care system for patients admitted with a primary diagnosis of HF was $482 million in 2013, accounting for 0.8% of hospital spending that year. The projected increase in spending by 2030 is postulated in the realm of $720 million. Including the patients with HF as a secondary diagnosis, the cost estimate increases to $2.8 billion annually or around 1% of Canada’s GDP. The Canadian Institute of Health Indicators estimates the cost of an HF hospitalization in Canada to be approximately $10,000 based on data from 2016 with a long average length of stay of 8 days. This could mean over $40 million in savings simply related to hospitalizations alone with optimal sacubitril/valsartan use. Tackling the care gap caused by underutilization of medications for eligible patients with HF provides an opportunity to significantly reduce the cost to our Canadian health care system. This analysis highlights one approach by optimizing the use of sacubitril/valsartan in patients with HFpEF.

There are limitations to this analysis, most of which stem from calculated numbers being based on the assumption that treatment at the population level will translate into similar effectiveness reported by clinical trials. This is also fully dependent on patients being able to tolerate the drug at doses similar to those used in the PARADIGM-HF study with similar side effect profiles outside of the clinical trial setting. Indeed, efficacy rates may be overestimated if the HFpEF patient population has more adverse side effects or less clinical benefit than study participants. Encouragingly, it has been noted in previous observational studies of ACEI/ARB therapy that the observed real-world outcomes in terms of efficacy and safety are similar to those seen in trials, including in older adults. In addition, real-world eligibility of sacubitril/valsartan therapy may vary from estimates used in this study, based on the differences between the real-world clinical HFpEF patient population and study participants. There are limited published Canadian HF data available, and what is available was used where available to define the appropriate HF population. Most of the estimates for exclusions from the treatment population were based on the methodology from a published study in the United States by Fonarow et al. Conversely, the study population may underrepresent certain patient populations that were excluded in the clinical trial. The efficacy of the medication will also depend on the uptake and prescription of the drug by physicians taking care of patients with HF in Canada. Population data and HF prevalence were obtained from national databases and therefore are susceptible to response and reporting biases.

Estimates used regarding the number of patients in Canada receiving sacubitril/valsartan were based on sales data as well as dosage and compliance assumptions specific to Novartis Pharmaceuticals Canada Inc., which also manufacture Entresto (sacubitril/valsartan). The details for the derivation of these data were not specifically shared with the authors.

Conclusions

Evidence-based treatments for HF are well established and have resulted in important reductions in death and hospitalization. Given the high burden of HF and substantial costs to the Canadian health care system, it is of utmost importance that treatments with demonstrated benefits be used. As far as we are aware, this study is the first of its kind to illustrate the gap in sacubitril/valsartan therapy in the HF population. It also highlights the importance and potential impact of optimally prescribing current evidence-based medications using the example of available ARNI therapy in Canada. This is the first quantification of the magnitude of survival benefits at the population level in Canada, resulting from the optimal usage of sacubitril/valsartan therapy for patients with current Health Canada approved indications for treatment. The findings from this analysis suggest that a substantial number of deaths, hospitalizations, and HF readmissions could potentially be avoided by optimal usage of sacubitril/valsartan therapy in Canada. This emphasizes the importance of rapidly and appropriately implementing evidence-based medications into routine clinical practice, to achieve the best possible outcomes for patients with HF.

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Disclosures

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