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Original Article

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.

RÉSUMÉ

Contexte : L'insuffisance cardiaque (IC) avec diminution de la fraction d'éjection touche actuellement environ 50 % des 600 000 Canadiens qui sont atteints d'IC, et plus de 90 000 nouveaux cas de cette affection sont diagnostiqués chaque année. L'association sacubitril-valsartan (inhibiteur de la néprilysine et antagoniste des récepteurs de l'angiotensine) a démontré une efficacité supérieure à celle du traitement de référence au chapitre de la réduction de la mortalité d'origine cardiovasculaire et des hospitalisations dues à l'IC.

Méthodologie : L'ampleur potentielle des bienfaits du médicament au Canada en matière de prévention ou de report des décès et de

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 **P**rospective Comparison of

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

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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.

Résultats : Chez les 225 562 patients potentiellement admissibles au traitement, le médicament permettrait de prévenir 4 699 décès d'origine cardiovasculaire et premières hospitalisations pour cause d'IC, 3 698 réhospitalisations pour cause d'IC dans les 30 jours suivant la sortie de l'hôpital et 2 820 décès toutes causes confondues. À l'échelle nationale en 2018, 27 267 patients ont été traités par l'association sacubitril-valsartan. Cela représente environ 12 % de la population admissible au traitement selon les calculs s'appliquant au Canada.

Conclusions : Les résultats de cette analyse permettent de penser que beaucoup de décès, d'hospitalisations et de réhospitalisations pour cause d'IC pourraient être évités par suite de la mise en œuvre optimale du traitement par l'association sacubitril-valsartan au Canada. Sous cet éclairage, force est de constater l'importance que revêt l'intégration rapide et appropriée des pharmacothérapies factuelles à la pratique clinique courante, dans l'optique d'une démarche visant à obtenir les meilleurs résultats possible chez nos patients atteints d'IC et à réduire le lourd fardeau de cette affection au Canada.

ARNI with **A**CEI to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (PARADIGM-HF) trial.[12] 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 (NYHA) 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.[13] 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.[14-18]

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.[16]

A US-based study by Fonarow et al.[19,20] 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.[21] The direct costs of treating HF alone in 2012 were estimated at CAD$2.89 billion per year, approximately 1% of Canada's GDP.[22] 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.[19,23] 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.[10,24] 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.[19] 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%.[2,23,25,26] We decided to use a prevalence of 70% for NYHA class II or III symptoms based on estimates from the current published literature.[2,23,25,26] 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).[19,23] To account for intolerance expected with ACEI, 7% of patients were removed and finally, based on the degree of adverse events reported from the

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 population	225,562	53,137	84,080	8681	7943	21,494	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

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, **P**rospective Comparison of **ARNI** with **ACEI** to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure.

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, standardized to 12 months (actual median follow-up was 27 months), was derived from the absolute risk reductions (ARR) observed in the PARADIGM-HF trial. This was examined for the composite primary outcome from PARADIGM-HF, which was CV death and first HF hospitalization, as well as CV death, first HF hospitalization, all-cause mortality, and 30-day HF readmission. Based on an ARR of 4.7% for the primary composite outcome, the NNT was 48. The NNT for CV death was 70 (ARR 3.2%), for first HF hospitalization 80 (ARR 2.8%), for all-cause mortality 80 (ARR 2.8%), and for 30-day HF readmission 61 (ARR 3.7%).[12,27] The potential number of deaths, hospitalizations, and hospital readmissions prevented as a result of optimal usage of sacubitril/valsartan as per current approved usage in Canada (patients with HFrEF, left ventricular ejection fraction $\leq$40%, and NYHA class II or III symptoms) were estimated using methods previously described.[19] A sensitivity analysis was also conducted using an analysis of extremes method to calculate upper and lower estimates of benefit using $\pm$20% relative differences for the number of eligible patients and estimates of risk reduction.[28]

Finally, the number of patients in Canada receiving sacubitril/valsartan was estimated based on territorial sales analysis data (number of units sold) provided by IQVIA solutions Canada Inc. for the January through December 2018 data period, as well as a dosage assumption specific to Novartis Pharmaceuticals Canada Inc. Adherence assumptions were derived by Novartis from Strömberg et al.[29] This information was used to estimate the actual real-world benefit of sacubitril/valsartan in Canada using the same methods as noted above (ie, applying the NNT to the estimated number of patients receiving sacubitril/valsartan in Canada).

Results

The HF prevalence in Canada was determined to be 3.70% (Table 1). This prevalence was applied to the 18,903,250 Canadians 40 years and older to approximate the total number of patients with HF in the country at 699,420. The calculated eligible population when considering the Health Canada monograph for sacubitril/valsartan and potential other exclusions was 225,562 (32%) of the patients with HF (see Fig. 1). For each province, the prevalence of HF varied between 3.35% and 4.58%. Reported potential preventable outcomes were calculated based on available national and provincial eligible population data (Table 1). Prescription of sacubitril/valsartan to all eligible patients with HF in Canada would potentially prevent 4699 (3007-6767) CV deaths and first HF hospitalizations per year (Table 2). There would also potentially be prevention of an estimated 2820 (1804-4059) all-cause mortality events, 3698 (2367-5325) 30-day HF readmissions, and 3222 (2062-4640) CV deaths (Table 1).

The actual estimated number of patients receiving sacubitril/valsartan nationally in 2018 was 27,267.[30] This represents approximately 12% of the calculated eligible population for this therapy in Canada. The percentage of eligible patients prescribed sacubitril/valsartan at the provincial level ranged from 3% to 18%. Therefore, the actual benefit to patients for the composite primary outcome of CV death and first HF hospitalization is approximately 568 (364-818) vs the potential benefit of 4699 (3007-6767) for Canada overall (Table 2). This care gap was calculated for all examined outcomes for Canada overall (Table 2).

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 health care 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

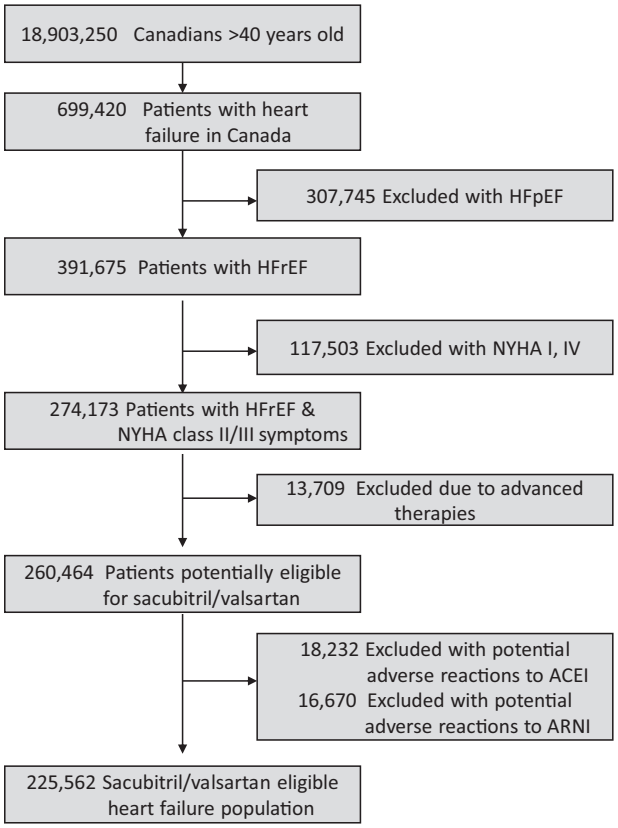

Figure 1. Angiotensin receptor neprilysin inhibition (ARNI) eligibility flow diagram. Derivation of the population of patients with HFrEF eligible for sacubitril/valsartan. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

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.[37] Based on the 2016 Report on the Health of Canadians from the Heart and Stroke Foundation, the 30-day readmission rate is 21%.[9] 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.[38,39] Although the length of inpatient hospital stays is declining for patients with HF, the absolute number of patients admitted to hospital is increasing.[40] 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.[41] 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.[10,42] 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.[43]

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.[44] 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.[14] Patient-related factors can include comorbidities leading to intolerance or contraindications.[45] Physician-related factors include medical inertia, focus on symptom relief rather than mortality, and fear of adverse events.[14,46] 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

	Actual benefit (range) (population 27,267)	Potential benefit (range) (population 225,562)
CV death or 1st HF hospitalization (NNT = 48)	568 (364-818)	4699 (3007-6767)
CV death (NNT = 70)	390 (250-562)	3222 (2062-4640)
HF hospitalization (NNT = 80)	340 (218-490)	2820 (1804-4059)
All-cause mortality (NNT = 80)	340 (218-490)	2820 (1804-4059)
30-day HF readmission (NNT = 61)	447 (286-644)	3698 (2367-5325)

CV, cardiovascular; HF, heart failure; NNT, number needed to treat.

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antagonist) needs to be titrated to maximally tolerated doses, which can often take 4-6 months to accomplish.[3] 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.[14] 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.[3] 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.[46,47] At present, most patients with HF are cared for by primary care physicians and general internists.[46,48]

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.[49] 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.[50-52] 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.[53] 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.[40] 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.[54] 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 HFrEF.

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 HFrEF 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.[55] 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 HFrEF 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.[19] Conversely, the study population may underrepresent certain patient populations that were excluded in the clinical trial.[19] 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 (sacubirtril/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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