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Original Article

Use of Sacubitril/Valsartan Prior to Primary Prevention Implantable Cardioverter Defibrillator Implantation

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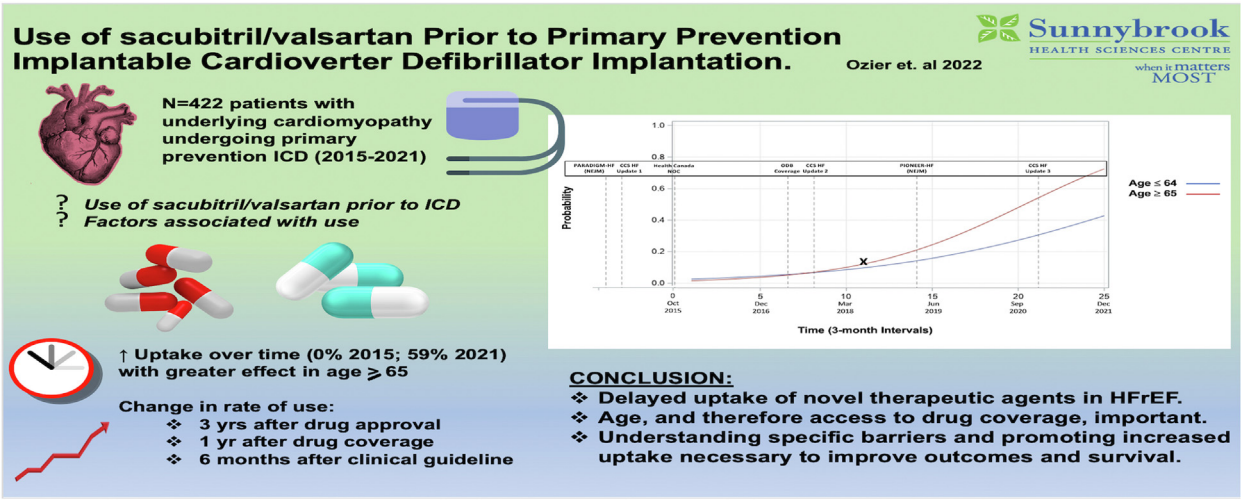

ABSTRACT

Background: Implantable cardioverter defibrillators (ICDs) are an adjunct to guideline-directed medical therapy for heart failure with reduced ejection fraction. The uptake of sacubitril/valsartan in this population is not well described. We report the uptake and factors associated with sacubitril/valsartan use in patients with left ventricular dysfunction undergoing ICD implantation.

Methods: A retrospective chart review was performed on all patients with left ventricular dysfunction who underwent *de novo* primary prevention ICD implantation between October 2015 and December 2021 (n = 422) at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. Pre-procedure sacubitril/valsartan use was determined. Lo-

RÉSUMÉ

Contexte : Les défibrillateurs cardioverteurs implantables (DCI) sont un complément au traitement médical fondé sur les lignes directrices chez les patients atteints d'insuffisance cardiaque à fraction d'éjection réduite. L'adoption de l'association sacubitril-valsartan chez ces derniers n'est pas bien caractérisée. Nous abordons l'adoption de cette association médicamenteuse ainsi que les facteurs associés à son utilisation parmi les patients présentant une dysfonction ventriculaire gauche chez qui un DCI est implanté.

Méthodologie : Nous avons effectué un examen rétrospectif des dossiers médicaux de tous les patients atteints d'une dysfonction ventriculaire gauche chez qui un DCI a été implanté *de novo* en

The implantable cardioverter defibrillator (ICD) is an important adjunct to guideline-directed medical therapies (GDMTs) in patients with heart failure and a reduced ejection fraction (HFrEF),[1,2] with pivotal clinical trials demonstrating a reduction in sudden cardiac death and an improvement in overall survival.[3,4] A dramatic increase in the armamentarium of drugs comprising GDMTs has occurred since the publication of the initial landmark ICD trials.[5]

Sacubitril/valsartan is a newer heart failure (HF) therapy that is currently considered a pillar in the treatment of HFrEF.

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gistic regression analysis was performed to examine factors associated with sacubitril/valsartan use. A Bayesian estimator of abrupt change was employed to determine a time period in which a change in the rate of sacubitril/valsartan use occurred.

Results: Loop diuretic use (odds ratio [OR] = 2.20) and higher severity of New York Heart Association class symptoms (OR = 1.62) were associated with sacubitril/valsartan use. Sacubitril/valsartan use increased during the study period, to 59% in December 2021. This increase was larger among those aged ≥ 65 years (OR = 1.09). A change in the rate of sacubitril/valsartan use occurred 3 years after drug approval, 1 year after provincial drug coverage became available, and 6 months after being strongly recommended in clinical guidelines.

Conclusions: In a contemporary cohort of ICD patients, sacubitril/valsartan use increased between 2015 and 2021, notably in those aged ≥ 65 years and after government drug coverage became available. Understanding barriers to sacubitril/valsartan use in ICD patients is recommended to improve clinical outcomes and survival in this population.

prévention primaire entre octobre 2015 et décembre 2021 (n = 422) au Sunnybrook Health Sciences Centre, situé à Toronto (Ontario), au Canada. Nous avons recensé les cas où l'association sacubitril-valsartan avait été utilisée avant l'intervention, et une analyse de régression logistique a été réalisée pour mettre en lumière les facteurs associés à l'utilisation de l'association sacubitril-valsartan. Un estimateur bayésien de changement soudain a servi à déterminer si le taux d'utilisation de l'association sacubitril-valsartan avait changé au cours de cette période.

Résultats : L'utilisation de diurétiques de l'anse (rapport de cotes [RC] = 2,20) et une plus grande intensité des symptômes selon la classification de la New York Heart Association (RC = 1,62) se trouvaient associées à l'utilisation de l'association sacubitril-valsartan. Au cours de la période à l'étude, le taux d'utilisation de l'association sacubitril-valsartan s'est accru, atteignant 59 % en décembre 2021. Cette augmentation était plus marquée parmi les patients de 65 ans ou plus (RC = 1,09). L'association sacubitril-valsartan a vu son taux d'utilisation changer trois ans après avoir été homologuée, un an après avoir été inscrite sur la liste des médicaments remboursés par le régime d'assurance médicaments provincial et six mois après avoir été fortement recommandée dans les lignes directrices cliniques.

Conclusions : Au sein d'une cohorte contemporaine de patients ayant reçu un DCI, l'association sacubitril-valsartan a connu une hausse d'utilisation entre 2015 et 2021, notamment chez les patients âgés de 65 ans ou plus et à la suite de son inscription sur la liste des médicaments remboursés par le régime public d'assurance médicament. Il serait souhaitable de cerner les obstacles à l'utilisation de l'association sacubitril-valsartan chez les patients qui reçoivent un DCI afin d'améliorer les résultats cliniques et la survie au sein de cette population.

In 2014, the **P**rospective Comparison of **AR**Ni With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (PARADIGM-HF) trial demonstrated a 2.8% absolute reduction for HF hospitalization, and a 2.8% improvement in overall survival in HF patients, compared to standard medical therapy.[6] The benefits of sacubitril/valsartan extend to patients regardless of age, severity of left ventricular (LV) dysfunction, and presence of ICDs.[6,7] In 2014, the Canadian Cardiovascular Society (CCS) HF management focused update provided a conditional recommendation on sacubitril/valsartan use.[8] Health Canada approval was granted in October 2015.[9] Coverage under the Ontario Drug Benefit plan (which provides drug cost coverage for Ontarians ≥ 65 years of age) was obtained in April 2017.[10] Recommendations on sacubitril/valsartan use were further expanded upon and were upgraded to a "strong" recommendation in the 2017 CCS HF guidelines[2]; additional evidence on its safety was provided with the publication of the Com**pa**r**i**son **o**f Sacubitril/Valsarta**n** Versus **E**nalapril on **E**ffect on Nt-P**r**o-Bnp in Patients Stabilized From an Acute **H**eart **F**ailure Episode (PIONEER-HF) trial in 2019.[11]

Clinical guidelines for ICD implantation state that all patients undergoing ICD implantation require at least 3 months of optimal medical therapy, but they are not explicit as to what constitutes optimal medical therapy.[1] One can hypothesize that a large proportion of patients undergoing ICD implantation would receive sacubitril/valsartan prior to ICD implantation, as sacubitril/valsartan use was recommended for patients with a reduced ejection fraction (EF) and symptoms of heart failure. This hypothesis is bolstered by the fact that sacubitril/valsartan has important benefits in ICD candidates, including an improvement in EF such that some individuals no longer meet EF-based criteria for ICDs,[12] and is associated with a reduction in the risk of ventricular arrhythmia and subsequent ICD therapies.[7,13]

As sacubitril/valsartan is a newer HF therapy, its uptake and factors associated therewith, in patients undergoing ICD implantation, are not well defined.[14]. Given the specific benefits of sacubitril/valsartan in ICD patients,[7,12,13] this knowledge may identify a care gap and improve the clinical care of a well-defined, high-risk patient population with LV dysfunction. Furthermore, study into the uptake of this novel HF agent will provide insight as to whether past practices of delayed uptake of evidence-based cardiovascular therapies[15] continue to exist, and specifically, will examine this in a cohort of patients receiving a costly non-pharmacologic/device therapy. Herein, we report the uptake

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Ethics Statement: Ethics approval was obtained from the Sunnybrook Health Sciences Centre Research Ethics Board.

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See page 98 for disclosure information.

Table 1. Baseline characteristics

Variables	Sacubitril/valsartan (yes; n = 130)	Sacubitril/valsartan (no; n = 292)	*P*
Age, y, mean (SD)	68.4 (11.8)	68.2 (11.4)	0.83
Gender (female)	32 (24.6)	52 (17.8)	0.11
Prior MI ischemic CM (yes)	61 (46.9)	187 (64.0)	**0.001**
AF (yes)	37 (28.5)	89 (30.5)	0.68
Severity of EF, mean (SD)	26.0 (6.2)	27.3 (5.4)	**0.04**
Severity of CHF symptoms (NYHA class)			**< 0.0001**
1	18 (13.9)	105 (36.3)	
2	88 (67.7)	122 (42.2)	
3	24 (18.5)	62 (21. 5)	
Hypertension (yes)	88 (67.7)	188 (64.4)	0.51
Systolic blood pressure, mm Hg, mean (SD)	123.8 (19.6)	125.1 (17.5)	0.49
Creatinine clearance, mL/min, mean (SD)	71.8 (32.7)	70.5 (37.3)	0.74
Loop diuretic (yes)	94 (72.3)	159 (54.5)	**0.0005**
Device type			**0.0006**
BiV	70 (53.9)	105 (36.0)	
Non BiV	60 (46.2)	187 (64.0)	
Duration of LV dysfunction $\geq$ 1 year (yes)	105 (80.8)	224 (76.7)	0.35
QRS duration, msec, mean (SD)	147.0 (30.9)	133.2 (29.7)	**< 0.0001**
Potassium, mmol/L, mean (SD)	4.4 (0.5)	4.4 (0.5)	0.93
Beta-blocker (yes)	124 (95.4)	268 (91. 8)	0.18
MRA (yes)	75 (57.7)	111 (38.0)	**0.0002**
Digoxin (yes)	5 (3.9)	15 (5.1)	0.56
ACEi/ARB (yes)	0 (0)	247 (84.6)	< 0.0001

Values are n (%), unless otherwise indicated. Boldface indicates statistical significance.

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BiV, biventricular; CHF, congestive heart failure; CM, cardiomyopathy; EF, ejection fraction; LV, left ventricle; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.

of, and factors associated with, the use of sacubitril/valsartan in patients with HFrEF undergoing primary-prevention ICD implantation.

Methods

Sunnybrook Health Sciences Centre (SHSC) is a large regional tertiary cardiac care centre in Toronto, Ontario, Canada. All patients undergoing *de novo* ICD implantation for primary prevention between October 1, 2015 and December 31, 2021 were included in this single-centre retrospective study. Patients undergoing ICD implantation during an inpatient admission were excluded, as they may not have had the opportunity to receive evidence-based HF therapies prior to ICD implantation. Patients with an EF > 35%, a known history of an inherited arrhythmia (eg, long QT, Brugada, hypertrophic cardiomyopathy) or other cardiomyopathy (eg, sarcoidosis, muscular dystrophy) were excluded due to a lack of evidence for sacubitril/valsartan use in these populations. Given the lack of reliability among practitioners in assigning New York Heart Association (NYHA) class,[16] and overlap in classification of NYHA I/II class,[17] the primary analysis included all patients with NYHA I-IV symptoms. A sensitivity analysis limited to patients with NYHA II-IV symptoms was performed, as the CCS HF guidelines recommended sacubitril/valsartan use with HF symptoms.[2]

Hospital (Sunnycare, version 7.5.4.4; Sovera, version 10.4.1) and ICD clinic (Paceart Optima System, version 1.8.269.0; Medtronic, Minneapolis, MN) electronic medical records were reviewed for each patient, to determine demographics, clinical characteristics, and details of the implanted device. Medication use, electrocardiographic characteristics, resting heart rate, and blood pressure were obtained at the day of implantation. Biochemical data were determined with pre-procedure bloodwork performed no earlier than 3 months prior to the procedure date.

Descriptive statistics, including mean and standard deviation for continuous variables, and frequency and percentage for categorical variables, were reported for patients that received sacubitril/valsartan prior to ICD insertion and those who did not.

A multivariable binary logistic regression model was fitted to identify independent predictors of sacubitril/valsartan use. Variables in the model included patient clinical characteristics and medication use. The time period an individual was included in the study (expressed per 3 months of the study period) was included as a variable in the model, as time since approval of a drug is well known to be associated with its uptake.[15,18,19] Furthermore, because government-funded drug coverage for sacubitril/valsartan became available during the study period for those patients aged $\geq$ 65 years, a "time by age" interaction term was also included in the model to assess whether the influence of time on the odds of sacubitril/valsartan prescription was influenced by age (or vice versa). Odds ratios (ORs), with 95% confidence intervals (95% CIs), and *P*-values were reported, and statistical analysis was conducted at a significance level of 0.05 for a 2-tail test, using SAS software, version 9.4 (SAS Institute, Cary, NC,).

A **B**ayesian **E**stimator of **A**brupt Change, **S**easonality, and **T**rend (BEAST) was used to capture trends and abrupt changes in the rate of sacubitril/valsartan use during the study period in order to provide context to the impact of specific milestones (ie, guidelines recommendations, advent of availability of government drug cost coverage) on a change in the prescription of sacubitril/valsartan. The mathematical details of BEAST have been described in detail previously.[20] Briefly, BEAST combines several models into an average model (Bayesian model average), instead of relying on a single model to detect changes in time series. It allows for estimation of the probability for abrupt changes at any given point in time, as opposed to other change point algorithms that simply identify whether a change point is present or not (binary result). The BEAST modeling of receiving sacubitril/valsartan in the 3-month time series was performed using the package "Rbeast" v0.9.3 in R software v1.2.5 (R Foundation, Vienna, Austria).

Table 2. Factors associated with sacubitril/valsartan use

Variables	Odds ratio	95% CI	*P*
Time (3-mo intervals)	1.13	1.06, 1.20	**0.0001**
Age (≥ 65 vs < 65 y)	0.33	0.08, 1.31	0.12
Time (3-mo intervals) and age (≥ 65 y)	1.09	1.01, 1.19	**0.03**
Gender (females vs males)	1.10	0.56, 2.16	0.79
Prior MI ischemic CM (yes vs no)	0.61	0.34, 1.08	0.09
AF (yes vs no)	0.48	0.26, 0.90	**0.02**
Severity of EF	0.96	0.92, 1.00	0.07
Severity of CHF symptoms (NYHA class)	1.62	1.06, 2.45	**0.02**
Systolic blood pressure, mm Hg	1.01	0.99, 1.02	0.53
Creatinine clearance	1.01	1.00, 1.01	0.13
Loop diuretic (yes vs no)	2.20	1.20, 4.04	**0.01**
Device type (BiV vs non BiV)	1.58	0.91, 2.75	0.10
Duration of LV dysfunction ≥ 1 y (yes vs no)	1.84	0.96, 3.51	0.07
MRA (yes vs no)	1.68	0.97, 2.91	0.07

AF, atrial fibrillation; BiV, biventricular; CHF, congestive heart failure; CI, confidence interval; CM, cardiomyopathy; EF, ejection fraction; LV, left ventricle; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

Ethics approval was obtained from the Sunnybrook Health Sciences Centre Research Ethics Board.

Results

This study included 422 patients (mean age = 68 years, standard deviation = 12 years, 80% male). Of the 130 patients on sacubitril/valsartan, 57 (44%) received a low dose (24/26 mg), 37 (28%) received a medium dose (49/51 mg), and 36 (28%) received a high dose (97/103 mg). In total, 59% of the cohort had a prior history of coronary artery disease, and 78% had at least 1 year of LV dysfunction. Beta-blockers were used by 93% of patients. Angiotensin-converting enzyme inhibitors (ACEis), angiotensinogen receptor blockers (ARBs), or sacubitril/valsartan were used in 89% of patients. Mineralocorticoid receptor antagonists (MRAs) were used by 44% of patients. Patients receiving sacubitril/valsartan more frequently had a nonischemic etiology of HF, a lower mean EF, and a wider baseline QRS. They reported higher rates of NYHA ≥ 2 symptoms, were more frequent users of loop diuretics and MRAs, and received a higher proportion of biventricular defibrillators (Table 1). Sacubitril/valsartan use increased during the study period, from 0% in 2015 to 59% in 2021, with 50% of patients aged < 65 years, and 61% aged ≥ 65 years receiving sacubitril/valsartan in 2021.

The results from multivariable analysis examining the factors associated with sacubitril/valsartan use in patients undergoing *de novo* primary prevention ICD implantation are presented in Table 2. In comparison to patients who were not on loop diuretics, patients receiving loop diuretics had 2.20 higher odds (95% CI = 1.20-4.04) of sacubitril/valsartan use. Patients with a higher NYHA class (OR = 1.62; 95% CI = 1.01-1.19) were more likely to be prescribed sacubitril/valsartan, and those with a history of atrial fibrillation were less likely to be prescribed sacubitril/valsartan (OR = 0.48; 95% CI = 0.26-0.90). Examination of change in use of sacubitril/valsartan over time, on average, revealed that sacubitril/valsartan use increased over the study period (OR = 1.13 per 3-month interval; 95% CI = 1.06-1.20). Furthermore, a 2-way interaction was found between time and age of patients, suggesting that the increasing use of sacubitril/valsartan over the study period was higher in patients aged ≥ 65 years, compared to those aged < 65 years (OR per 3-month interval = 1.09; 95% CI = 1.01-1.19; Fig. 1).

Using the BEAST model, a change point in the probability of being prescribed sacubitril/valsartan was detected during the 3-month interval between April 1 and June 30, 2018 (Fig. 1). This time point was approximately 3 years after drug approval, 1 year after from the advent of availability of provincial drug coverage, and 6 months after strong recommendations in clinical guidelines.

A sensitivity analysis limiting the cohort to individuals with NYHA class II-IV symptoms (n = 299) was performed (see Supplemental Appendix S1). Sacubitril/valsartan use increased during the study period, with 67% of this subgroup receiving sacubitril/valsartan in 2021—64% of patients aged < 65 years and 68% aged ≥ 65 years. Findings similar to those reported above were observed when the cohort was limited to patients with NYHA class II-IV symptoms, but as expected with the reduced sample size, statistical significance of some findings was no longer demonstrable.

Discussion

This single-centre, retrospective cohort study described the factors associated with sacubitril/valsartan use in patients undergoing primary prevention ICD implantation. Several important findings are demonstrated in this work. First, increased use of sacubitril/valsartan occurred well after the publication of its landmark clinical trial, the publication of recommendations within guidelines, and the advent of availability of provincial drug coverage. Second, although clinical factors reflecting symptomatic HF were strongly associated with sacubitril/valsartan prescription, nonclinical factors, including time since the advent of availability and age ≥ 65 years, both reflecting the impact of access to provincial drug coverage, were important predictors of sacubitril/valsartan use.

Our findings are consistent with prior work from various jurisdictions demonstrating suboptimal uptake of GDMT in HFrEF patients,[21-24] and a delay in uptake of pharmacologic therapies in general.[15,18-22,25] The care gap observed during earlier periods and in younger individuals in this study has important consequences, as the suggestion has been made that optimizing sacubitril/valsartan use in eligible HFrEF patients in Canada could reduce HF-associated hospitalizations and HF-associated deaths by 15%,[24] leading to major cost-savings for the healthcare system and increased longevity for patients.

Multiple factors likely played a role in the delayed uptake of sacubitril/valsartan use in this cohort. We suspect that clinical factors were unlikely to be the dominant reasons for delayed drug use, as the odds for receipt of sacubitril/valsartan was highest in patients with clinical HF. Underutilization due to lack of drug tolerability secondary to hypotension or renal dysfunction is less plausible, as systolic blood pressure, potassium level, and creatinine clearance were similar in the groups that did vs did not receive sacubitril/valsartan. Furthermore, the increasing use of sacubitril/valsartan with time argues against low drug use due to lack of patient

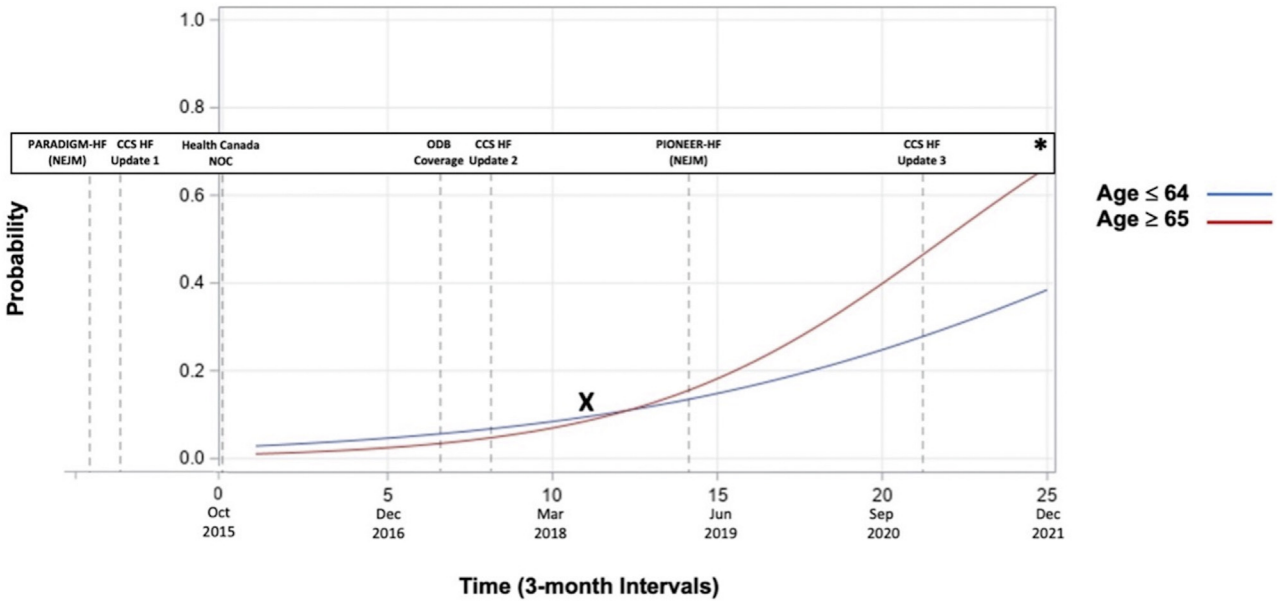

Figure 1. Probability of sacubitril/valsartan use during the study period, stratified by age (in years). **X** denotes the results of Bayesian change-point analysis, which revealed a statistically significant change in the probability of receiving sacubitril/valsartan that occurred during the 3-month segment from April 1 to June 30, 2018. CCS HF Update 1, Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update[8]; CCS HF Update 2: Comprehensive Update of the CCS Guidelines for the Management of Heart Failure[2]; CCS HF Update 3, CCS/Canadian Heart Failure Society Guidelines Update: Defining a New Pharmacologic Standard of Care for HFrEF [Heart Failure with Reduced Ejection Fraction][5]; Health Canada NOC, Health Canada Notice of Compliance for Sacubitril/Valsartan, Oct 2, 2015[9]; ODB Coverage, Ontario Drug Benefits addition of sacubitril/valsartan to provincial formula, Apr 27, 2017[10]; PARADIGM-HF, **P**rospective Comparison of **ARN**i With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure [6]; PIONEER-HF, Com**p**ar**i**son **o**f Sacubitril/Valsarta**n** Versus **E**nalapril on **E**ffect on Nt-P**r**o-Bnp in Patients Stabilized From an Acute **H**eart **F**ailure Episode[11]; Dec, December; Jun, June; Mar, March; Oct, October; Sep, September.

tolerability, as a dramatic change in clinical characteristics favouring drug tolerability during the study period is unlikely to have occurred. Lack of expert opinion is also less likely, as guideline recommendations were available prior to an observed increase in the rate of sacubitril/valsartan prescription. We were unable to account for the impact of the COVID-19 pandemic on physician practice and patient uptake of new drug therapies in this study, and so we cannot eliminate the influence of the pandemic on the uptake of this drug.

One possibility is that physicians do not consider that being on sacubitril/valsartan is necessary prior to ICD implantation, as data on the efficacy of ICDs were available prior to the advent of this drug.[3,4] Another possibility is that treating physicians may estimate that the benefits of ICDs and cardiac resynchronization therapy (CRT) outweigh those provided by sacubitril/valsartan (and given the low rate [44%] of MRA use in this cohort, possibly pharmacologic therapy in general), and therefore, they may defer initiating or optimizing this and other pharmacologic agents until after ICD insertion has taken place. Harmonization of ICD and HF guidelines may be necessary to optimize the use and timing of drug and device therapy in patients with HFrEF.

The increased odds of drug prescription with time, and the differential rate of prescription of sacubitril/valsartan in individuals aged $\geq$ 65 years vs $<$ 65 years highlight the importance of drug coverage on drug utilization. As sacubitril/valsartan is equally efficacious in patients regardless of age,[6] a lower rate of use in patients aged $<$ 65 years may quite possibly prevent a large subset of high-risk individuals from profiting from the benefits associated with this drug. Ensuring equitable access to this essential medication, and others of its kind, in a younger population with severe HFrEF, is important, given the chronic nature of this disease and the fact that the drug benefits are seen regardless of the age of onset.

Several limitations to our work merit consideration. First, coming from a single-centre study, our data may reflect local physician practice, which might limit the generalizability to other settings. Our work still has merit, as the patient population was similar to those reported in HF trials, and our physician referral base included a large number of physicians in different practice settings (office- and/or hospital-based general cardiologists and HF specialists) and locales (urban and rural). Second, although we collected data on drug prescription, data on adherence, including initiation and subsequent discontinuation prior to ICD insertion (for example due to transient hypotension), and initiation post-ICD implantation, were not uniformly available. As well, patient preference for drug use was not captured in our analysis.

Third, our sample size is relatively small, and so we may not have had sufficient power to identify all statistically significant predictors associated with the use of sacubitril/valsartan. Indeed, many of our statistically nonsignificant predictors barely crossed unity. Our approach, however, allowed collection of important granular clinical data (creatinine, electrolytes, and blood pressure) that impact decisions to prescribe sacubitril/valsartan, as well as data on drug use in patients aged $<$ 65 years. Although a prospective study might

have permitted more complete data collection, the associated Hawthorne effect would impact prescribing practices and prevent insight into the "natural history" of physician prescribing patterns for sacubitril/valsartan in clinical practice.

Conclusions

In this contemporary cohort of patients undergoing primary prevention ICD insertion, increasing use of sacubitril/valsartan was observed, notably in those aged $\geq$ 65 years and after the advent of availability of drug coverage. Understanding specific barriers and promoting its use in this population is recommended to improve clinical outcomes and survival in this high-risk patient population.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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