CJC Open ■ (2023) 1–7

Original Article

Use of Guideline-Directed Medical Therapy in Patients Aged 80 Years or Older With Heart Failure With Reduced Ejection Fraction

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ABSTRACT

Background: Guideline-directed medical therapy (GDMT) reduces morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF). Use of GDMT is recommended in all adults with HFrEF, but it is potentially underutilized in patients with advanced age. This study sought to characterize use of GDMT in octogenarians and nonagenarians with HFrEF and identify barriers to initiation and uptitration.

Methods: This retrospective cohort study included patients aged 80-99 years at 3 heart failure clinics in the Lower Mainland region of British Columbia, Canada. Patients with a left ventricular ejection fraction $\leq$ 40% and heart failure hospitalization $<$ 12 months were included.

RÉSUMÉ

Contexte : Le traitement médical recommandé dans les lignes directrices réduit la morbidité et la mortalité chez les patients atteints d'insuffisance cardiaque à fraction d'éjection réduite (ICFER). Ce traitement est préconisé chez tous les adultes atteints d'ICFER, mais pourrait être sous-employé chez les patients d'âge avancé. Cette étude visait à caractériser son utilisation chez les octogénaires et les nonagénaires atteints d'ICFER et à repérer les obstacles à l'initiation d'un tel traitement et à l'augmentation de la dose.

Méthodologie : Cette étude de cohorte rétrospective regroupait des patients âgés de 80 à 99 ans de trois cliniques traitant l'insuffisance cardiaque dans la région du Lower Mainland, en Colombie-Britannique,

Heart failure (HF) places a significant burden on the healthcare system. An estimated 50,000 Canadians are newly diagnosed with HF each year, and more than $2.8 billion Canadian dollars (CAD) are spent annually on HF-related complications.[1] Within the Fraser Health region of British Columbia, Canada, the incidence of HF in men and women aged $\geq$ 80 years is 41 per 1000 persons, compared to 10 per 1000 among those aged 65-79 years.[2] Fraser Health is responsible for the delivery of hospital and community-based health services to approximately 2 million people from Burnaby to the Fraser Canyon on the traditional, ancestral, and unceded territories of the Coast Salish and Nlaka'pamux Nations in British Columbia. The prevalence of HF in octogenarians and nonagenarians is projected to steadily rise, as this population is expected to increase by 54% over the next decade.[3]

The 2021 Canadian Cardiovascular Society/Canadian Heart Failure Society HF guidelines update recommends 4 standard therapies for all patients (regardless of age) with HF with reduced ejection fraction (HFrEF) in the absence of contraindications.[4] The 4 guideline-directed medical therapies (GDMTs) include the following: (i) one of an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor; (ii) a beta-blocker; (iii) a mineralocorticoid receptor antagonist (MRA); and (iv) a sodium-glucose cotransporter 2 (SGLT2) inhibitor. These therapies have been demonstrated in landmark clinical trials to reduce HF-related hospitalizations and mortality and improve symptoms and quality of life.[5-17] However, the average age of patients in these clinical trials was approximately 61-65 years, with very limited inclusion of patients aged $\geq$ 80 years.

Despite the lack of representation in these clinical trials, efficacy data on GDMTs are often extrapolated as though they

Received for publication October 31, 2022. Accepted January 3, 2023.

Ethics Statement: This study was approved by the University of British Columbia Clinical Research Ethics Board and the Fraser Health Research Ethics Board via a harmonized review (H21-02568).

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See page 6 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.01.002

Data were collected between September 2019 and August 2021, for up to 24 months from the initial clinic visit.

Results: A total of 91 patients were included. The mean age was 85 years, and the mean left ventricular ejection fraction was 30%. About 50% of patients had New York Heart Association class II symptoms. Throughout the study follow-up period, approximately 91% of patients were on a beta-blocker, 72% were on a renin-angiotensin system (RAS) inhibitor, 31% were on a mineralocorticoid receptor antagonist (MRA), and 4% were on a sodium-glucose cotransporter 2 (SGLT2) inhibitor. The target dose was achieved in 19% of patients on a beta-blocker, 7% on an RAS inhibitor, 11% on an MRA, and 100% on an SGLT2 inhibitor. Frequent barriers to GDMT initiation and/or uptitration were renal dysfunction, hypotension, and hyperkalemia.

Conclusions: The levels of use of RAS inhibitors and beta-blockers in patients aged 80-99 years with HFrEF were reasonable, whereas the levels of use of MRAs and SGLT2 inhibitors were low. Achievement of target doses of GDMT was rare, owing to common adverse effects.

au Canada. Des patients présentant une fraction d'éjection ventriculaire gauche (FEVG) $\leq$40 % et hospitalisés en raison d'une insuffisance cardiaque dans les 12 derniers mois ont été inclus dans l'étude. Les données ont été recueillies entre septembre 2019 et août 2021, jusqu'à 24 mois après la visite initiale à la clinique.

Résultats : Au total, 91 patients ont été inclus dans l'étude. Leur âge moyen était de 85 ans, et la FEVG moyenne, de 30 %. Environ 50 % des patients présentaient des symptômes de la classe II de la New York Heart Association. Pendant toute la période de suivi de l'étude, environ 91 % des patients étaient traités par un bêtabloquant, 72 % par un inhibiteur du système rénine-angiotensine (SRA), 31 % par un antagoniste des récepteurs minéralocorticoïdes (ARM) et 4 % par un inhibiteur du cotransporteur du glucose-sodium de type 2 (SGLT2). La dose cible a été atteinte chez 19 % des patients traités par un bêtabloquant, 7 % de ceux traités par un inhibiteur du SRA, 11 % de ceux recevant un ARM et 100 % des sujets recevant un inhibiteur du SGLT2. Les obstacles fréquents à l'instauration du traitement médical recommandé dans les lignes directrices ou à l'augmentation de la dose étaient la dysfonction rénale, l'hypotension et l'hyperkaliémie.

Conclusions : Les taux d'utilisation des inhibiteurs du SRA et des bêtabloquants chez les patients âgés de 80 à 99 ans présentant une ICFER étaient raisonnables, tandis que les taux d'utilisation des ARM et des inhibiteurs du SGLT2 étaient faibles. L'atteinte des doses cibles préconisées dans le traitement médical recommandé dans les lignes directrices était rare en raison des effets secondaires courants.

apply equally well to octogenarians and nonagenarians. However, the real-world evidence regarding actual use in this patient population is limited. Several barriers to using GDMTs in older adults remain.[18-20] Due to pharmacodynamic changes, older patients are at higher risk of common adverse effects of GDMTs, including hypotension, bradycardia, renal impairment, and electrolyte disturbances, as well as drug-drug interactions due to polypharmacy. Further, age-related comorbidities, such as frailty and cognitive impairment, may be actual or perceived barriers to initiation or uptitration of GDMT. Conversely, appropriate GDMTs in non-frail patients aged $\geq$ 80 years may be underutilized due to an overestimation of the risk of harm, or an underestimation of the benefit regarding symptoms and quality of life. Other factors, such as increased pill burden or financial concerns, may negatively affect medication utilization and adherence in older adults, regardless of frailty or comorbidity. Despite these concerns, many patients aged $\geq$ 80 years with HFrEF may be undertreated with GDMT due to a potential overestimation of the risk of therapy or an underestimation of the benefit of therapy.[18]

The objective of the current study was to evaluate and characterize the utilization of GDMTs, as well as identify barriers to initiation and uptitration of GDMTs, in a cohort of octogenarians and nonagenarians with HFrEF who were receiving care from specialized HF clinics.

Methods

Study design

This retrospective cohort study included all patients receiving care from 1 of 3 specialized HF clinics within the Fraser Health region of British Columbia. The clinics are based at the Royal Columbian Hospital in New Westminster, the Jim Pattison Outpatient Care and Surgery Centre in Surrey, and the Abbotsford Regional Hospital and Cancer Centre in Abbotsford, all in British Columbia. Each HF clinic is an outpatient secondary care cardiac clinic located in a hospital or ambulatory care centre. These multidisciplinary clinics provide specialized care to patients referred for a clinical diagnosis of new or worsening HF irrespective of ejection fraction. Each clinic is staffed by a rotating group of cardiologists, as well as other healthcare professionals such as nurses, nurse practitioners, pharmacists, dietitians, and social workers. The purpose of the clinics is to provide evidence-based care to patients with HF, to reduce mortality and hospitalizations, and improve symptoms and quality of life. This study was approved by the University of British Columbia Clinical Research Ethics Board and the Fraser Health Research Ethics Board via a harmonized review (H21-02568).

Study population

Included were patients aged 80-99 years with a left ventricular ejection fraction (LVEF) of 40% or less. Patients were also required to have been hospitalized with a primary diagnosis of an acute HF exacerbation within the 12 months prior to being seen in the HF clinic, and they were required to have had 2 or more visits at the HF clinic. Patients with HF with preserved ejection fraction (LVEF $>$ 40%) were excluded. Patients were identified based on International Classification of Diseases, 10th Revision, code I50 (HF) and electronic health record coding in Meditech (Medical Information Technology, Inc., Westwood, MA).

Data collection

Data on eligible patients were collected retrospectively from their electronic health record (Meditech) from

September 1, 2019 to August 31, 2021 (up to 24 months of follow-up). The following data were collected: age, sex, weight, LVEF, etiology of HF, New York Heart Association (NYHA) classification, medical comorbidities (hypertension, coronary artery disease, atrial fibrillation, stroke, chronic kidney disease, and diabetes mellitus), and relevant vitals and laboratory values. Data on use of the 4 standard GMDTs were collected at each visit (drug name, drug dose, drug route, and frequency of drug administration), as well as any documented barriers to the use or uptitration of GDMT. The barriers to initiation or uptitration of GDMT were based on any documented reason (free-form or other documentation) in the patient's electronic health record. These barriers did not have specific definitions or criteria, as the goal was to capture any perceived barriers to use or uptitration of GDMT. All data were collected by one researcher (M.G.) using a standardized data collection form.

Objectives

The primary objective of this study was to determine the proportion of patients aged 80-99 years with HFrEF who were prescribed 3 of the 4 standard GDMTs, as follows: a renin-angiotensin system (RAS) inhibitor (eg, an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor-neprilysin inhibitor), a beta-blocker, and an MRA over the study follow-up period. SGLT2 inhibitors were excluded from the primary objective, as they have been endorsed only recently by HF guidelines. Additional objectives included the proportion of patients on each of the 4 standard GDMTs, including SGLT2 inhibitors, as well as the proportion of patients on the target dose of each agent. The target dose for each medication was based on the recommended doses provided in the 2021 Canadian Cardiovascular Society/Canadian Heart Failure Society HF guidelines update.[4] Data on any documented barriers to initiation or uptitration of the 4 GDMTs (eg, adverse drug reactions, contraindications, nonadherence, potential harm perceived to outweigh potential benefit) were also collected.

Statistical analysis

Descriptive statistics were used to report patient characteristics and medication utilization. Categorical values were reported as frequencies with percentages, and continuous variables were reported as means with standard deviations or medians with interquartile ranges based on the distribution. All analyses were performed with Excel (Microsoft, Redmond, WA).

Results

A total of 91 patients were included in this study. Reasons for excluding patients are outlined in Figure 1. Among the excluded patients, a high proportion had HF with preserved ejection fraction (161 of 241; 67%). Patient characteristics are included in Table 1. The mean age was 85.2 ± 3.9 years, with a mean LVEF of 30.4%. Most patients had NYHA class II or III symptoms. A majority of patients (53.8%) had HFrEF secondary to myocardial ischemia. Data were available for 75 patients (82% of the overall population) at 1-3 months, 66 patients (73% of the overall population) at 4-6 months, and 54 patients (59% of the overall population) at 7-24 months.

Overall medication utilization is included in Figure 2. At the initial clinic visit, 23 patients (25%) were prescribed the 3 primary GDMTs (ie, a RAS inhibitor, a beta-blocker, and an MRA). The highest utilization was of beta-blockers, at 92%, whereas no patients were on an SGLT2 inhibitor. Over the entire study period, the proportion of patients prescribed a beta-blocker and an MRA remained fairly consistent, at 89%-92% and 31%-32%, respectively. Although an initial increase occurred in the proportion of patients prescribed a RAS inhibitor up to the 6-month follow-up visit (79%), this proportion decreased during the 7-to-24-month period (67%). The proportion of patients prescribed an SGLT2 inhibitor increased to 7% by the end of the study period.

The proportions of patients on the target dose of each of the GDMTs are included in Figure 3. Overall, the level of achievement of target doses of GDMTs was low. The proportion of patients achieving target dosing of a RAS inhibitor

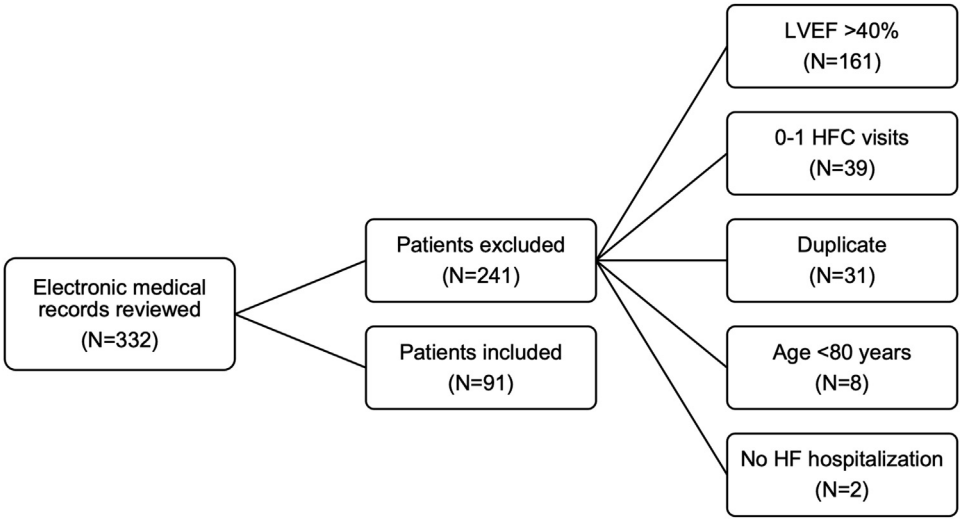

Figure 1. Study flow diagram. HF, heart failure; HFC, heart failure clinic; LVEF, left ventricular ejection fraction.

Table 1. Baseline characteristics (N = 91)

Characteristic	Value
Age, y	85.2 ± 3.9
Male sex	55 (60.4)
Weight, kg	72.8 ± 19.7
Systolic BP, mm Hg	120.4 ± 18.2
Diastolic BP, mm Hg	66.5 ± 11.1
Heart rate, bpm	72.3 ± 14.6
Serum creatinine, μmol/L	145.0 ± 81.2
eGFR, mL/min per 1.73 m^2	43.5 ± 19.5
Serum sodium, mmol/L	138.1 ± 4.0
Serum potassium, mmol/L	4.2 ± 0.6
Hemoglobin A1c, %	6.4 ± 1.1
LVEF, %	30.4 ± 6.7
Etiology of heart failure	
Ischemic	49 (53.8)
Nonischemic	32 (35.2)
Mixed ischemic and nonischemic	8 (8.8)
Unknown	2 (2.2)
NYHA classification	
I	4 (4.4)
II	45 (49.4)
III	39 (42.9)
IV	3 (3.3)
Comorbidities	
Hypertension	77 (84.6)
CAD	59 (64.8)
CKD	59 (64.8)
Atrial fibrillation	58 (63.7)
Diabetes mellitus	37 (40.7)
Stroke	20 (22.0)

Values are presented as mean ± standard deviation or number (percentage).

BP, blood pressure; bpm, beats per minute; CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

was variable. It increased from a baseline of 11% to a peak of 17% during the 4-to-6-month period, but then declined to 7% in the 7-to-24-month period. The proportions of patients on a target dose of a beta-blocker and an MRA were stable, at approximately 19% and 11%, respectively, throughout the study period. All patients prescribed an SGLT2 inhibitor were on the target dose.

Barriers to initiation and uptitration of GDMTs are detailed in Table 2. Patients could have had more than one barrier. Almost half of patients (48%) had renal dysfunction. The other most commonly documented barriers were hypotension and hyperkalemia.

Discussion

This study demonstrated that the use of GDMTs in patients aged ≥ 80 years was variable depending on the agent, but low overall. Throughout the study period, only up to roughly one-third of patients were prescribed the 3 primary GDMTs, specifically, a RAS inhibitor, a beta-blocker, and an MRA. This pattern was due primarily to a low level of utilization of MRAs, at approximately 31%. The most highly utilized of any of the GDMTs was beta-blockers, at approximately 90%, and the level of use of RAS inhibitors was also relatively high, at > 65%, with variability across the study period. Not unexpectedly, the level of use of SGLT2 inhibitors was low, as it was only recently added as a GDMT. Appropriate use of GDMTs should be considered a priority in older patients with HFrEF to reduce adverse HF-related outcomes—irrespective of a patient's advanced age—as it has been shown to reduce the risk of HF hospitalization, which may be more important to some older patients, vs a mortality benefit. This point is germane to the present study, as all included patients had a previous HF hospitalization. Conversely, as articulated in a review by Butrous and Hummel,[18] "The conventional viewpoint that elderly patients with HF value symptom control and quality of life over longevity is not always true," as there is evidence that some older patients value the survival benefit of GDMT.

Our study population was similar to that in the Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen (CHECK-HF) study, which examined the use of the 3 primary GDMTs (RAS inhibitor, beta-blocker, and MRA) in 2009 patients aged 80 years or older with HFrEF at 34 outpatient clinics in the Netherlands in 2013-2016.[21] At baseline, the average age was 84 years; 42% were female; the mean LVEF was 30%; the mean estimated glomerular filtration rate (eGFR) was 45 mL/min per 1.73 m^2, and about half the population had NYHA class II symptoms. As in our study, the 3 primary GDMT agents were prescribed to about 30% of patients in the CHECK-HF study. The level of use of RAS inhibitors was similar in the present study to that in the CHECK-HF study (67%-79% vs 73%), whereas the level of use of beta-blockers was higher in

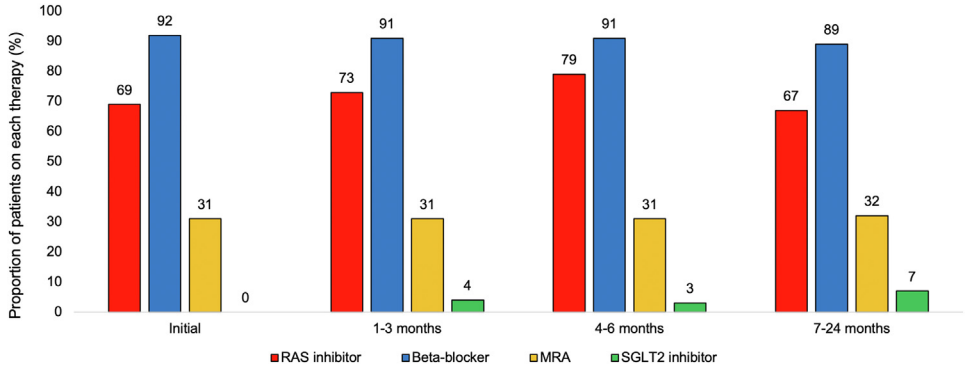

Figure 2. Proportion of patients on each of the guideline-directed medical therapies. MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2.

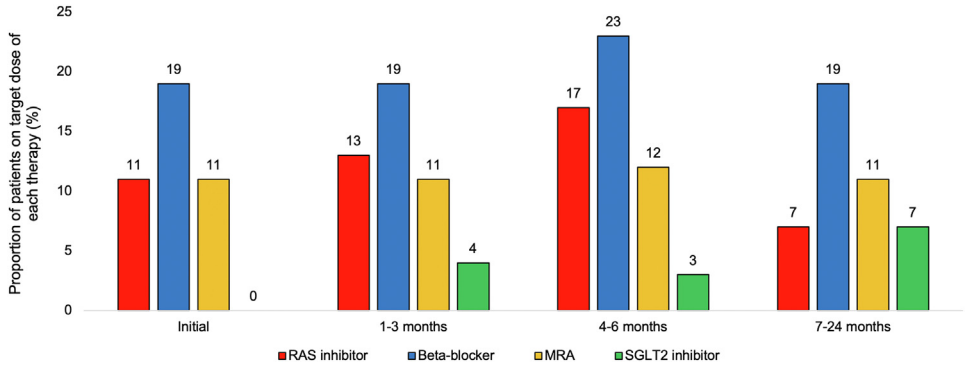

Figure 3. Proportion of patients on the target dose of each of the guideline-directed medical therapies. MRA, mineralocorticoid receptor antagonist; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2.

the present study vs the CHECK-HF study (89%-92% vs 78%). This difference may have been due to a higher number of patients in the present study having atrial fibrillation (64% vs 34%). Conversely, the level of use of MRAs was lower (31%-32% vs 52%) despite similar baseline renal function in both populations.

The **Cha**nge the **M**anagement of **P**atients With **H**eart **F**ailure (CHAMP-HF) study included 3518 patients from 150 primary care and cardiology clinics in the US between 2015 and 2017.[22] This study did not specifically enrol older patients, as the mean age was 66 years. Use of drug therapy was reported based on eligibility (eg, treated, with a contraindication, or untreated without a contraindication). The level of use of RAS inhibitors and MRAs among eligible patients was similar to that in the present study, at 73% and 33%, whereas the level of use of beta-blockers was lower at 67%. Fewer than 30% of patients prescribed an RAS inhibitor or a beta-blocker were on the target dose, which is comparable to the proportion in the present study, whereas 77% were on the target dose of an MRA vs roughly 32% in the present study. Despite a lower mean age, only 22% of the cohort were on all 3 of the primary GDMTs (RAS inhibitor, beta-blocker, and MRA), which is less than the percentage in the present study. In adjusted logistic regression models, older age, renal insufficiency, lower blood pressure, and a recent HF hospitalization were independently associated with a lower level of medication utilization and dose, which supports the relatively low overall level of use of GDMTs in the present study. Both the CHECK-HF and CHAMP-HF studies provide supporting evidence that the current use of GDMTs in older persons has remained relatively unchanged since these studies were conducted in 2013-2017.

Table 2. Barriers to initiation or uptitration of guideline-directed medical therapies (N = 91)

Barrier	n	%
Renal dysfunction	44	48.4
Hypotension	36	39.6
Hyperkalemia	22	24.2
Dizziness	17	18.7
Hospitalization	15	16.5
Orthostatic hypotension	14	15.4
No blood work or vitals available	14	15.4
Bradycardia	12	13.2
Patient request	12	13.2
Falls risk	11	12.1
Nonadherence	11	12.1
Frailty	10	11.0
Cough	7	7.7
Syncope	6	6.6
LVEF improved	5	5.5
Fatigue	5	5.5
Gastrointestinal disorder	2	2.2
Allergy	1	1.1
Amyloidosis	1	1.1
Angioedema	1	1.1
Aortic stenosis	1	1.1
Second-degree AV block	1	1.1
Urinary retention	1	1.1

AV, atrioventricular; LVEF, left ventricular ejection fraction,

To our knowledge, this study was the first to evaluate the use of SGLT2 inhibitors in octogenarians and nonagenarians with HFrEF. However, the overall level of utilization was low, at 7%. This level may have been due to slow uptake in practice, as the first SGLT2 inhibitor trial conducted specifically in HFrEF patients was initially published in November 2019.[16] As well, the population in the present study was older (85 years vs 66-67 years), with a lower level of baseline renal function (eGFR, 44 vs 62-66 mL/min per 1.73 m^2) vs that in patients in the **Dapa**gliflozin and Prevention of Adverse Outcomes in **H**eart **F**ailure (DAPA-HF) and the **Emp**agliflozin Outcome **T**rial in Patients With Chr**o**nic Hea**r**t Failure and a **Reduced** Ejection Fraction (EMPEROR-Reduced) trials.[16,17] Therefore, clinicians may have been more reluctant to initiate SGLT2 inhibitors in patients aged $\geq$ 80 years, as they were not well represented in these trials. Finally, publicly funded insurance coverage for SGLT2 inhibitors specifically for HFrEF became available in the province only by 2022 (after the data-collection period), although coverage was available for patients with diabetes.

The barriers to initiation and uptitration of GDMT identified in the present study were expected, given the age of the population. These may explain the low level of use of MRAs, as many of the documented barriers are common adverse effects, such as renal dysfunction, hypotension, and hyperkalemia. Some of the barriers, such as frailty, falls risk, and nonadherence, are common among older persons but can be mitigated through formal assessments and interventions by healthcare professionals specializing in the care of older patients. Therefore, this unmet need among older patients who attend specialized HF clinics supports the need for

development of cardiac clinics specifically designed for patients with advanced age or frailty, staffed by clinicians with specialized training in both cardiology and geriatrics. Of note, most of the data-collection period overlapped with the COVID-19 pandemic. Thus, the uptitration of GDMTs may have been halted due to patients' inability to attend clinic visits or have routine blood work.

The concept of guideline-recommended target doses in older patients is controversial, as most of the patients included in the clinical trials were younger (mean age: 61-65 years). Therefore, whether achievement of these target doses is clinically appropriate in those aged 80 years or older is questionable. Based on our results, we advocate the use of lower doses of each of the 4 GDMTs, to maximize the benefit of reducing HF-related hospitalizations among patients aged $\geq$ 80 years. Our study identified remaining opportunities to improve utilization of MRAs and SGLT2 inhibitors in this patient population. Thus, clinicians should consider a lower dose of a RAS inhibitor to facilitate concomitant use of an MRA and SGLT2 inhibitor. Further, clinicians should accept the fact that most older patients with HFrEF may be able to achieve only a maximally tolerated dose of each GDMT (as opposed to the target dose), and that achievement of target doses should be pursued only in select patients who tolerate each medication without evidence of adverse effects, primarily hypotension and renal impairment. The risk of hypotension and bradycardia is of particular concern to older persons, as these may contribute to falls and other sequelae.

This study characterized the real-world use of GDMTs in a contemporary cohort of patients aged $\geq$ 80 years with HFrEF at 3 specialized HF clinics. However, it included a small sample size, as a high proportion of screened patients had HF with preserved ejection fraction (161 of 332; 49%). Thus, the results of this study are generalizable to only patients with HFrEF, which represents only a fraction of patients aged 80 years or older with HF. The study was not designed to assess the use of MRAs and SGLT2 inhibitors in patients with HF with preserved ejection fraction. We did not collect data on frailty, as patients seen in these clinics are not routinely assessed for frailty using a validated tool. Further, we did not specifically collect data on dementia or cognitive impairment at baseline. The study design did not permit the determination of any association between GDMT use and clinical outcomes, such as mortality or HF hospitalization. Yet, a cohort study of 2045 older patients with HFrEF in Korea revealed that use of a RAS inhibitor and a beta-blocker, as compared to no therapy, was associated with a 48% relative lower risk of all-cause mortality among patients aged $\geq$ 80 years.[23] A potential for underreporting of barriers to initiation or uptitration of therapy was also present in the current study, as it relied on the completeness of the documentation in the electronic health record. The usage and dosing of diuretic therapy, in combination with use of RAS inhibitors and MRAs, may have contributed to some of the barriers (eg, hypotension, renal dysfunction), but such data were not collected as part of this study.

Conclusions

The findings of this study provide insight on the use of GDMT in octogenarians and nonagenarians with HFrEF in clinical practice. The level of use of RAS inhibitors and beta-blockers was reasonably high and was comparable to that in other studies, whereas the level of use of MRAs and SGLT2 inhibitors was low. Achievement of target doses of GDMT was rare, owing to common adverse effects, a finding that is not unexpected considering that these target doses were utilized in clinical trials with a younger population. Optimization of GDMT in patients with advanced age remains challenging, owing to factors that affect this patient population, such as hypotension and renal impairment. Therefore, clinicians should consider achieving maximally tolerated doses of GDMTs, as opposed to target doses, based on patient-specific factors. A need remains for randomized controlled trials to evaluate the safety and efficacy of GDMT specifically in patients aged $\geq$ 80 years with HFrEF.

Funding Sources

Funding for the publication fee was supported by internal start-up funding at the Faculty of Pharmaceutical Sciences at the University of British Columbia. The authors have no other funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

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