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ORIGINAL RESEARCH ARTICLE

Differences in Pharmacological Treatment of Heart Failure Among Persons with or without Major Cognitive Disorder: A Cross-Sectional Study Based on National Registries in Sweden

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Abstract

Introduction Comorbidities are common among older people, and during the last decade, a strong association between heart failure (HF) and cognitive impairment has been found. As much as 40–50% of individuals with HF will also have some degree of cognitive impairment. Previous studies report an undertreatment for some cardiovascular diseases in patients with major neurocognitive disorder (NCD).

Objective The aim of this present study was to explore differences in pharmacological treatment of HF in individuals diagnosed with HF with or without comorbidity of major NCD.

Methods This study combined data from three different Swedish national registers: the Swedish National Patient Register, the Swedish registry for cognitive/dementia disorders (SveDem), and the Swedish Prescribed Drug Register. A logistic regression model including variables for age, sex, major NCD, and nursing home residency was used to analyze associations between drug use and major NCD.

Results We found a lower prevalence of filled prescriptions of renin-angiotensin system (RAS) inhibitors, β-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs) among patients with major NCD. Living in a nursing home was associated with lower prevalence of RAS inhibitors, BBs, digitalis glycosides, and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Females were found to have higher odds of using BBs, loop diuretics and digitalis glycosides, and lower odds of using RAS inhibitors and SGLT2 inhibitors than males.

Conclusion Our findings indicate that there is possible undertreatment among individuals with HF identified in specialized care with co-occurring major NCD. Major NCD was associated with less filled prescriptions of basal pharmacological treatments such as RAS inhibitors, BBs, and MRAs. Future research needs to not only investigate this relationship further but also focus on reasons for the undertreatment of HF and other comorbidities within this group.

1 Introduction

The prevalence of heart failure (HF) in industrialized countries is estimated to be 1–3% in the general adult population and mortality remains high despite a slight improvement in prognosis [1]. This is concluded to be due to an increasing proportion of the total population being older and an increase of survival following major adverse cardiovascular events [2]. HF is indeed predominant

Key Points

Our findings indicate that there might be undertreatment of heart failure (HF) among individuals with major neurocognitive disorder. Since a large fraction of individuals who are diagnosed with HF are also reported to be cognitively impaired, our findings consequently affect a significant number of individuals.

Future research needs to not only investigate this relationship further but also focus on reasons for undertreatment of HF and other comorbidities within this group.

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among the older populations and its prevalence within this group is estimated to near double by 2030 [3].

Comorbidities are common among older people, and during the last decade, a strong association between HF and cognitive impairment has been found. As much as 40–50% of individuals with HF will also have some degree of cognitive impairment and this etiology is thought to be multifactorial [4, 5]. However, the exact mechanisms behind the association between HF and cognitive impairment are still unclear and further studies are needed to investigate this relationship.

This knowledge gap resonates into clinical guidelines of HF treatment where specific recommendations for comorbidity with cognitive impairment are currently lacking [6]. In addition, individuals with cognitive impairment are regularly excluded from clinical trials, including trials investigating HF or its treatment. Nevertheless, as there are no specific treatment guidelines for HF in individuals with co-occurring cognitive impairment, current guidelines are also still used in the case of cognitive impairment but without firm evidence.

Drugs serving as the current foundation for pharmacological treatment of HF in 2021 European Society of Cardiology (ESC) guidelines include a renin-angiotensin system (RAS) inhibitor, β-blocker (BB), mineralocorticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors [7]. These recommendations address HF with reduced ejection fraction (HFrEF). Although adverse drug events such as bradycardia, dizziness, hypotension, hyperkalemia, and renal impairment might affect the ability to adhere to guidelines [8], previous studies have found that individuals with cognitive impairment or major neurocognitive disorder (NCD) are less likely to receive evidence-based treatment for some cardiovascular diseases [9–11]. Furthermore, individuals with concomitant HF and cognitive impairment have a high risk of drug-related hospital admissions [12], and suboptimal pharmacological treatment of HF is a contributing reason for these admissions [13]. In order to achieve optimal treatment of HF, it is important to use all the recommended drugs, if tolerated, and this also accounts for patients with major NCD. Thus, the aim of this present study was to explore differences in pharmacological treatment of HF in individuals diagnosed with HF with or without comorbidity of major NCD in a national cohort based on three nationwide registries in Sweden.

2 Methods

2.1 Study Population

The present cross-sectional study comprised individuals aged 65 years or older on 31 December 2019 diagnosed with HF according to the Swedish National Patient Register. As a first step, patients with major NCD were identified from 2007 to 2019 through three different databases: (1) the Swedish registry for cognitive/dementia disorders (SveDem), including both basal registrations and the specific nursing home module; (2) the National Patient Register, which contains information from specialized care units, using International Classification of Diseases (ICD) codes F00, F01, F02, F03, G30 or G31 (i.e. subtypes of major NCD; and (3) the Swedish Prescribed Drug Register, based on any dispensing record of anti-dementia drugs, i.e. subgroup N06D according to the Anatomical Therapeutic Chemical (ATC) classification. Each individual found in those registries was matched by age and sex to a reference person from the Total Population Register. Patients with cognitive, personal, behavioral, or neurodegenerative conditions covered by ICD codes F05, F06, F07, and G32 were excluded from the selection of reference individuals to avoid including individuals with other diagnoses that might result in impaired cognition. These procedures, initially conducted to compare psychotropic drug use in relation to major NCD in a previous study [14], resulted in a dataset of 175,923 individuals. That population was cross-linked with the National Patient Register to find any records of HF, i.e. ICD code I50, diagnosed before 1 January 2020. This final step resulted in 22,827 individuals with HF, who comprised the sample for the present study.

2.2 Drug Use, Comorbidities, and Nursing Home Residency

The study population was interlinked with the National Patient Register, the Swedish Prescribed Drug Register, and the National Register of Care and Social Services for the Elderly and Persons with Impairments to obtain information about diagnoses, drug use, and nursing home residency, respectively. Records of filled prescriptions and social service efforts were transformed from a row format for each event into dichotomized variables. Drug dispensing data were sorted by individual substances according to the ATC system, and we identified drug use as at least one filled prescription from 1 July 2019 to 31 December 2019. Individual substances were divided into six different categories of HF medicines: RAS inhibitors (C09), recommended BBs at HF (bisoprolol, carvedilol and metoprolol) [7], MRAs (C03D), loop diuretics (C03C), digitalis glycosides (C01AA), and

SGLT2 inhibitors (A10BK). ESC guidelines in use in 2019 recommended RAS inhibitors, selected BBs, and MRAs as basic HF treatment for patients with HFrEF. Other drugs to be considered in selected patients with HFrEF are loop diuretics (recommended to reduce the signs and/or symptoms of congestion), and digitalis glycosides (an additional option in patients with remaining symptoms) [15]. SGLT2 inhibitors were included in this study, although they were not added to the guidelines until 2021 [7]. All individual substances within each category are presented in electronic Supplementary Table S1. We defined nursing home residents as persons with at least one monthly record of nursing home stay from 1 July 2019 to 31 December 2019.

2.3 Statistics

Drug use and comorbidities were summarized and presented as proportions. Pearson's Chi-square test or independent sample *t*-test were used to evaluate differences in proportions and means, respectively. Logistic regression was used to estimate associations between HF medicines and independent variables comprising major NCD, age, female sex, and nursing home residency. Results from the regression analyses are presented as odds ratios (ORs) with 95% confidence intervals and *p*-values. Age was treated as a continuous variable representing the OR per year. Cleaning of the registry data was carried out in Stata 17 (StataCorp LLC, College Station, TX, USA). During the subsequent data handling, IBM Statistics SPSS version 28 (IBM Corporation, Armonk, NY, USA) was used for descriptive and analytical statistics. A *p*-value of 0.05 was considered statistically significant.

2.4 Ethical Considerations

This study was approved by the Swedish Ethical Review Authority (registration number 2020-04663).

3 Results

The basic characteristics of the study population are presented in Table 1. The group with major NCD was older, with a mean age of 85.0 years compared with 84.7 years among individuals in the reference group ($p < 0.008$). Furthermore, the proportion of females was higher in the group with major NCD compared with the reference group ($p < 0.001$). The Swedish unit dose dispensing system was used by 75.1% of patients with major NCD and by 27.3% of the reference group ($p < 0.001$). A higher proportion lived in a nursing home among patients with major NCD compared with the reference group ($p < 0.001$).

The prevalence of HF medications among individuals with and without major NCD is presented in Table 2. There was a lower prevalence of RAS inhibitors ($p < 0.001$), BBs ($p < 0.001$), MRAs ($p < 0.001$) and SGLT2 inhibitors ($p = 0.004$) among individuals with major NCD compared with those in the reference group.

The lower prevalence of RAS inhibitors, BBs, and MRAs among patients with major NCD was also visible in the output from the logistic regression analysis (results of the logistic regression analysis including ORs are presented in full in Table 3). In addition, higher age was negatively associated with the use of RAS inhibitors, BBs, MRAs and SGLT2 inhibitors, but positively associated with the use of loop diuretics ($p < 0.001$ for all drug classes). Living in a nursing home was associated with a lower prevalence of RAS inhibitors ($p < 0.001$), BBs ($p < 0.001$), MRA ($p < 0.001$), digitalis glycosides ($p = 0.009$), and SGLT2 inhibitors ($p = 0.030$) [see Table 3].

Females had higher odds of using BBs ($p < 0.001$), loop diuretics ($p < 0.001$), and digitalis glycosides ($p < 0.001$) than males; the results were the opposite for RAS inhibitors ($p < 0.001$) and SGLT2 inhibitors ($p = 0.004$) [see Table 3].

Table 1 Study population characteristics

	Major NCD	Reference group	*p*-Value
Number of individuals	10,540	12,287	NA
Female sex	5744 (54.5)	6398 (52.7)	<0.001[a]
Age, years [mean ± SD]	85.0 ± 6.4	84.7 ± 6.7	0.008[b]
Dose dispensing of medicines	7918 (75.1)	3352 (27.3)	<0.001[a]
Nursing home residency	4463 (42.3)	1030 (8.4)	<0.001[a]

Data are expressed as *n* (%) unless otherwise specified

NCD neurocognitive disorder, *SD* standard deviation, *NA* not available

[a]Chi-square tests

[b]Independent sample t-tests

Table 2 Proportions of different drug classes/drugs among individuals with major NCD and reference individuals

	Major NCD	Reference group	*p*-Value[a]
Number of individuals	10,540	12,287	NA
RAS inhibitors	5941 (56.4)	8532 (69.4)	<0.001
BBs	6842 (64.9)	8879 (72.3)	<0.001
MRAs	1852 (17.6)	3014 (24.5)	<0.001
Loop diuretics	5927 (56.2)	6657 (54.2)	0.002
Digitalis glycosides	1043 (9.9)	1215 (9.9)	0.986
SGLT2 inhibitors	120 (1.1)	195 (1.6)	0.004

Data are expressed as *n* (%)

BBs β-blockers, *MRAs* mineralocorticoid receptor antagonists, *NCD* neurocognitive disorder, *RAS* renin-angiotensin system, *SGLT2* sodium-glucose linked transporter-2, *NA* not available

[a]Chi-square tests

Table 3 Multiple logistic regression analysis of factors associated with drug classes among people with heart failure

	OR	95% CI		*p*-Value
		Lower	Upper	
RAS inhibitors				
Major NCD	0.67	0.63	0.71	<0.001
Female sex	0.89	0.84	0.95	<0.001
Higher age[a]	0.97	0.96	0.97	<0.001
Nursing home residency	0.63	0.58	0.66	<0.001
BBs				
Major NCD	0.77	0.72	0.82	<0.001
Female sex	1.12	1.06	1.19	<0.001
Higher age[a]	0.98	0.97	0.98	<0.001
Nursing home residency	0.79	0.74	0.85	<0.001
MRAs				
Major NCD	0.69	0.65	0.75	<0.001
Female sex	1.00	0.94	1.07	0.964
Higher age[a]	0.97	0.96	0.97	<0.001
Nursing home residency	0.86	0.78	0.93	<0.001
Loop diuretics				
Major NCD	0.96	0.91	1.02	0.167
Female sex	1.20	1.13	1.26	<0.001
Higher age[a]	1.04	1.03	1.04	<0.001
Nursing home residency	1.40	1.30	1.50	<0.001
Digitalis glycosides				
Major NCD	1.04	0.95	1.15	0.381
Female sex	1.53	1.39	1.68	<0.001
Higher age[a]	1.00	0.99	1.01	0.832
Nursing home residency	0.86	0.76	0.96	0.009
SGLT2 inhibitors				
Major NCD	0.87	0.68	1.12	0.280
Female sex	0.70	0.55	0.89	0.004
Higher age[a]	0.88	0.86	0.91	<0.001
Nursing home residency	0.66	0.45	0.96	0.030

OR odds ratio, *CI* confidence interval, *BBs* β-blockers, *MRAs* mineralocorticoid receptor antagonists, *NCD* neurocognitive disorder, *RAS* renin-angiotensin system, *SGLT2* sodium-glucose cotransporter-2

[a]Per year

4 Discussion

This present cross-sectional study utilized Swedish national register data from 2019 to study the prevalence of filled prescriptions of pharmacological treatment for HF within a country-wide HF population of 22,827 individuals with or without co-occurring major NCD. The findings indicate that there might be undertreatment of HF in patients with major NCD within specialized care.

We found that filled prescriptions of basic HF treatment, i.e. RAS inhibitors, BBs, MRAs, and SGLT2 inhibitors were significantly lower among patients with a comorbidity of major NCD compared with patients with HF without a registered NCD diagnosis, using a Chi-square test. This was further confirmed for RAS inhibitors, BBs, and MRAs by the multiple logistic regression model looking at specific variables in relation to HF drug groups, where having major NCD was found to be associated with lower use of these drug categories. It should be noted that SGLT2 inhibitors were not recommended as treatment for HF until 2021 [7].

Our results are principally in line with previous published results from Swedish studies of older people with cognitive impairment. For example, Svahn and colleagues compared cardiovascular drug treatment for elderly people with cognitive impairment living in Swedish nursing homes over time, and found that although treatment had improved, there was an association between lower use of RAS inhibitors, BBs, and MRA, and increasing cognitive impairment [16]. Furthermore, Abramsson et al. [17] reported fewer filled prescriptions of MRAs for individuals with cognitive impairment, as well as for loop diuretics, for which the user proportion in our study was highest in the group with major NCD. Furthermore, their study did not find associations between cognitive score and RAS inhibitors or BBs.

Further studies on this particular topic are overall scarce, but a previous US study found that individuals with Alzheimer's disease and HF were less likely to get the recommended pharmacological treatment compared with individuals with HF only [18]. Moreover, an Australian study by Liu et al. [11] found associations between lower use of BBs, RAS inhibitors, and relevant drugs belonging to ATC classes C01 and C02 in patients diagnosed with major NCD compared with those without this condition.

It should be pointed out that in the present study, information regarding ejection fraction (EF) was not available and it is possible that there could hence be an uneven distribution of EF in the groups. In 2019, no treatment was recommended for HF with preserved EF (HFpEF) other than to alleviate symptoms and improve well-being [15]. If the proportion of HFpEF was higher in the group with major NCD, this could contribute to lower use of RAS inhibitors, BBs, and MRAs, and could also partly explain the finding in the Chi-square analysis that individuals with major NCD more often received loop diuretics. Another possible explanation for the higher proportion of this drug category in the group with major NCD could be that loop diuretics might be prescribed more to individuals with insufficient treatment of HF to improve their symptoms.

Other possible reasons for fewer filled prescriptions of guideline-recommended treatment among patients with major NCD could be intolerance due to comorbidities, polypharmacy, impaired renal function, and adverse reactions. Indeed, bradycardia and orthostatic hypotension are

associated with the use of BBs [19, 20], and hyperkalemia is commonly reported among individuals with HF using MRAs and RAS inhibitors [8]. In this study, we did not have access to clinical data such as blood pressure, pulse, glomerular filtration rate (GFR), or electrolyte status, which may affect the ability to adhere to guidelines. In line with this reasoning, major NCD has previously been found to be associated with an increased risk of nursing home placement [21], and indeed, a higher proportion of patients with major NCDs in the present study were living in a nursing home compared with the reference group. Other studies have reported that patients with major NCD have a higher level of comorbidity and an increased risk of acute organ dysfunction, which might partly explain the differences in prescribing found in this study [22, 23]. However, our finding that the Swedish unit dose dispensing system was used by 75% of patients with major NCD compared with 27% of individuals in the reference group might support the hypothesis of an undertreatment of HF among patients with major NCD, since it has previously been shown that patients receiving dose dispensing more often have poorer treatment quality in relation to guidelines [24].

Overall, the importance of an individual and clinical assessment must be underlined and taken into consideration when interpreting the results of this study.

There were differences between the groups in this study that ought to be addressed along with the results presented. There were significantly more individuals of female sex in the group with co-occurring major NCD, and being female was positively associated with filling prescriptions of BBs, loop diuretics, and digitalis glycosides, but negatively associated with filling prescriptions of RAS inhibitors and SGLT2 inhibitors. In line with these data, a study by Greene et al. found that prescriptions of BBs were more commonly, and RAS inhibitors less commonly, prescribed to females [25]. Furthermore, there are data indicating that women are more often prescribed diuretics for HF, while men are more frequently prescribed angiotensin-converting enzyme (ACE) inhibitors [26]. Among the possible reasons proposed are that women express more problems with edema and experience more adverse effects from ACE inhibitors in comparison with men [26]. There are descriptions in the literature of the differences between male and females in terms of responses and outcomes of RAS inhibitors, but no clinical guidelines are in place to support these differences [27]. For SGLT2 inhibitors, the literature describes a gender gap in the treatment of diabetes that could also possibly extend to HF [28]. A different aspect of the larger proportion of women found in the NCD group is that the prevalence of HFpEF is higher among women than men [29], which could, to some extent, explain the lower levels of prescriptions of recommended treatment according to the guidelines. However, in the regression analysis, the lower proportion of evidence-based treatment among patients with major NCD persisted when the model was adjusted for sex.

Another finding in the regression analysis was that higher age was found to be negatively associated with RAS inhibitors, BBs, MRAs, and SGLT2 inhibitors. An explanation for this could be that HFpEF prevalence increases with age [30]. Furthermore, being older could indicate increased sensitivity to standard HF treatment, such as orthostatic hypotension or kidney dysfunction, which can often be controlled with altered doses [7]. Moreover, there are reports of pharmacological undertreatment of older people across several conditions [31]. Nevertheless, the variable representing major NCD indicated a stronger association with having no filled prescriptions of the different HF drug classes compared with higher age (except for digitalis glycosides) in our logistic regression model.

4.1 Strengths and Limitations

The strengths of this present study include a nationwide sample of individuals with HF and their drug prescriptions recorded in both national and quality registers. Information on diagnosis through ICD codes was available in two of the registers used to identify the total population, while the third register utilized prescription data, which has been recognized as a valid method [32]. Despite our broad three-step inclusion process, it is nonetheless possible that some patients with major NCD who did not meet any of the inclusion criteria might have been selected as references, but we do not believe this had a considerable impact on the results. Moreover, the National Patient Register includes reports from specialized care units from all Swedish administrative regions. Thus, a comprehensive method was used to identify the population, although with generalizability limited to patients with HF identified within specialized care.

There are however some limitations that should be addressed. First, the included data consist of a study population created from a sample of patients with major NCD who were separated into groups with and without HF, and then comparing filled prescriptions between these groups. Ideally, the sample should have been selected based on individuals with HF, and thereafter creating groups of individuals with or without major NCD. We recognize a couple of possible consequences of this method of selection. For example, our study population was potentially older than the average person with HF without co-occurring major NCD, and could hence be in a later stage of HF and thus require additional pharmacological treatment. However, the opposite is also possible, in that there would be a decrease in pharmacological treatment, as mentioned previously in this Discussion section. Regardless, it should be noted that this is an uncertain factor in our study.

Furthermore, as previously mentioned, our data lack information on EF and New York Heart Association (NYHA) classes in individuals with HF. As we do not know the distribution of a specific HF diagnosis in terms of EF, we do not know how many individuals in our included sample ought to be prescribed RAS inhibitors, BBs, and MRAs solely due to their HF diagnosis. Furthermore, it can be assumed that individuals included in the study may have other diagnoses such as hypertension, diabetes, and ischemic heart disease, advocating for treatment with the included drug classes according to clinical guidelines.

SGLT2 inhibitors were not recommended as a treatment for HF in 2019, which explains the low prevalence of this drug class in our study. Since then, evidence for treatment with SGLT2 inhibitors has increased, and the guidelines from 2021 include SGLT2 inhibitors in the management of HF [7]. This should be considered when interpreting the results.

Filled prescriptions were identified as an indication of ongoing pharmacological treatment. Although the Swedish Prescribed Drug Register includes all prescriptions hitherto filled in outpatient pharmacies, we did not have information on the reason for prescription, dosage, or nonadherence, e.g. whether the filled prescription was actually used by the individual. We also did not have information on contraindications to drugs, history of adverse effects, drug interactions, or patient refusal. Lastly, it is possible that other factors could be contributing to the presented results, apart from the variables included in our analysis, for example socioeconomic status, additional comorbidities, or geographic differences; however, these were not within the scope of this study.

5 Conclusions

Our results indicate that there might be undertreatment of HF among individuals with major NCD, at least within specialized care. More specifically, basal pharmacological treatment of HF, such as RAS inhibitors, BBs, and MRAs, were found to be associated with less filled prescriptions among individuals with major NCD. Future research needs to not only investigate this relationship further but also focus on the reasons for the undertreatment of HF and other comorbidities within this group. It is of interest to further explore treatment trends within this patient group. Barriers for prescribing optimal HF treatment to patients with cognitive impairment could be explored though qualitative methods such as focus groups interviews.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-024-01153-6.

Declarations

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Conflicts of Interest Linda Rankin, Sofia Svahn, Jonas Kindstedt, and Maria Gustafsson declare they have no potential conflicts of interest that might be relevant to this work.

Author Contributions Conceptualization and design were performed by (including design of the analysis) MG, SS, LR and JK. Formal analysis was performed by SS and JK. Data collection was performed by JK. The first draft of the manuscript was prepared by LR. All authors contributed to reviewing and editing of the manuscript, and have read and approved the final manuscript.

Ethics Approval This study was approved by the Swedish Ethical Review Authority (registration number 2020-04663).

Availability of Data and Material The datasets generated and/or analyzed in the present study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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