Cardiology

HF and Intensive Care: Research Article

Cardiology 2023;148:27–37
DOI: 10.1159/000528505

Received: August 26, 2022
Accepted: November 28, 2022
Published online: December 5, 2022

The Optimization of Guideline-Directed Medical Therapy during Hospitalization among Patients with Heart Failure with Reduced Ejection Fraction in Daily Clinical Practice

Fanni Bánfi-Bacsárdi[a] Balázs Muk[a, b, c] Dávid Pilecky[d] Gábor Zoltán Duray[a] Róbert Gábor Kiss[a] Noémi Nyolczas[a, b, c]

[a]Department of Cardiology, Medical Centre, Hungarian Defence Forces, Budapest, Hungary; [b]Department of Adult Cardiology, Gottsegen National Cardiovascular Center, Budapest, Hungary; [c]Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary; [d]Department of Internal Medicine III, Klinikum Passau, Passau, Germany

Keywords
Guideline-directed medical therapy · Heart failure · Heart failure with reduced ejection fraction · Worsening heart failure · Pharmacotherapy

Abstract
Introduction: Hospitalization due to heart failure (HF) progression is associated with poor prognosis. This highlights the role of the implementation of guideline-directed medical therapy (GDMT) in improving the morbidity and mortality of patients with heart failure with reduced ejection fraction (HFrEF). There are limited data about the intrahospital applicability of GDMT in real-world circumstances. We aimed to assess retrospectively the use of cornerstone GDMT including RASi (ACEI/ARB/ARNI), βB, MRA, and SGLT2i treatment in a consecutive real-world HFrEF patient population admitted with signs and symptoms of HF to the HF Unit of a Hungarian tertiary cardiac center between 2019 and 2021. The independent predictors of therapy optimization and the applicability of new HFrEF medication (ARNI, SGLT2i, vericiguat) were also investigated. ***Methods:*** Statistical comparison of admission and discharge medication was accomplished with Fisher's exact test. The independent predictors of the introduction of triple therapy (RASi + βB + MRA) were analyzed using univariate and multivariate logistic regression. The proportion of patients eligible for vericiguat based on the inclusion and exclusion criteria of the VICTORIA trial was also investigated, as well as the number of patients suitable for ARNI and SGLT2i, taking into account the contraindications of application contained in the ESC 2021 HF Guidelines. ***Results:*** 238 patients were included. During hospitalization, the use of RASi (69% vs. 89%) (ACEI/ARBs [58% vs. 70%], ARNI [10% vs. 19%]), βBs (69% vs. 85%), and MRAs (61% vs. 95%) increased significantly ($p < 0.05$) compared to at admission, and the use of SGLT2i (3% vs. 11%) also rose ($p = 0.0005$). The application ratio of triple (RASi + βB + MRA; 43% vs. 77%) and quadruple (RASi + βB + MRA + SGLT2i; 2% vs. 11%) therapy increased as well ($p < 0.0001$). The independent predictors of discharge application of triple therapy revealed through multivariate logistic regression analysis were age, duration of hospitalization, eGFR, NTproBNP, and presence of diabetes mellitus. Sixty-eight percent of the cohort would have been suitable for vericiguat, 83% for ARNI, and 84% for SGLT2i. ***Conclusion:*** High rates of application of disease-modifying drugs are achievable among hospitalized HFrEF patients in severe clinical condition; thus, awareness of the need for their initiation must be raised.

Karger@karger.com
www.karger.com/crd

Correspondence to:
Fanni Bánfi-Bacsárdi, bacsardifanni@gmail.com

Karger

Introduction

Even nowadays, heart failure (HF) is of significant importance among cardiovascular diseases due to its high morbidity and mortality [1, 2]. Although treatment options for HF have expanded within the past decade, the related prognosis is still comparable to the life expectancies associated with many malignant neoplasms [3]. Patients admitted to hospital due to HF have a higher risk profile and poorer prognosis than chronic stable HF patients [4].

According to the results of the European Society of Cardiology (ESC) HF Long-Term Registry [5], 60% of patients suffering from HF have heart failure with reduced ejection fraction (HFrEF) [6]. Regarding the complex care of HFrEF, pharmacotherapy still represents the cornerstone of treatment, which invariably means the application of neurohormonal antagonists (angiotensin-converting enzyme inhibitor [ACEI], β blocker [βB], mineralocorticoid receptor antagonist [MRA]), which have proven efficacy at reducing morbidity and mortality. Additionally, based on the success of several randomized controlled clinical trials published within the last few years that assessed the efficacy and safety of new drugs (angiotensin receptor neprilysin inhibitor [ARNI] [7], sodium-glucose cotransporter-2 inhibitor [SGLT2i] [8–10], vericiguat [11]) with new pharmacological targets in HFrEF, the arsenal of potentially effective therapeutical options has expanded remarkably.

Although the current ESC Guidelines for the diagnosis and treatment of acute and chronic HF published in 2021 [12] give clear instructions about the initiation and use of disease-modifying pharmacotherapy in HFrEF, the application rate of the morbidity- and mortality-reducing drug regime remains undesirably low in real-world circumstances [13–15], especially regarding newly available life-saving medications (ARNI, SGLT2i). The application of guideline-directed medical therapy (GDMT) during the hospitalization of HF patients is rarely investigated [16]. In our research, we analyzed in a consecutive, real-world, hospitalized HFrEF patient population (1) the application rate of GDMT at hospital admission and discharge, (2) the independent predictors of discharge application of triple therapy (renin-angiotensin system inhibitor [RASi]: ACEI/ARB/ARNI + βB + MRA), and (3) the applicability of new HFrEF medication (ARNI, SGLT2i, vericiguat).

Materials and Methods

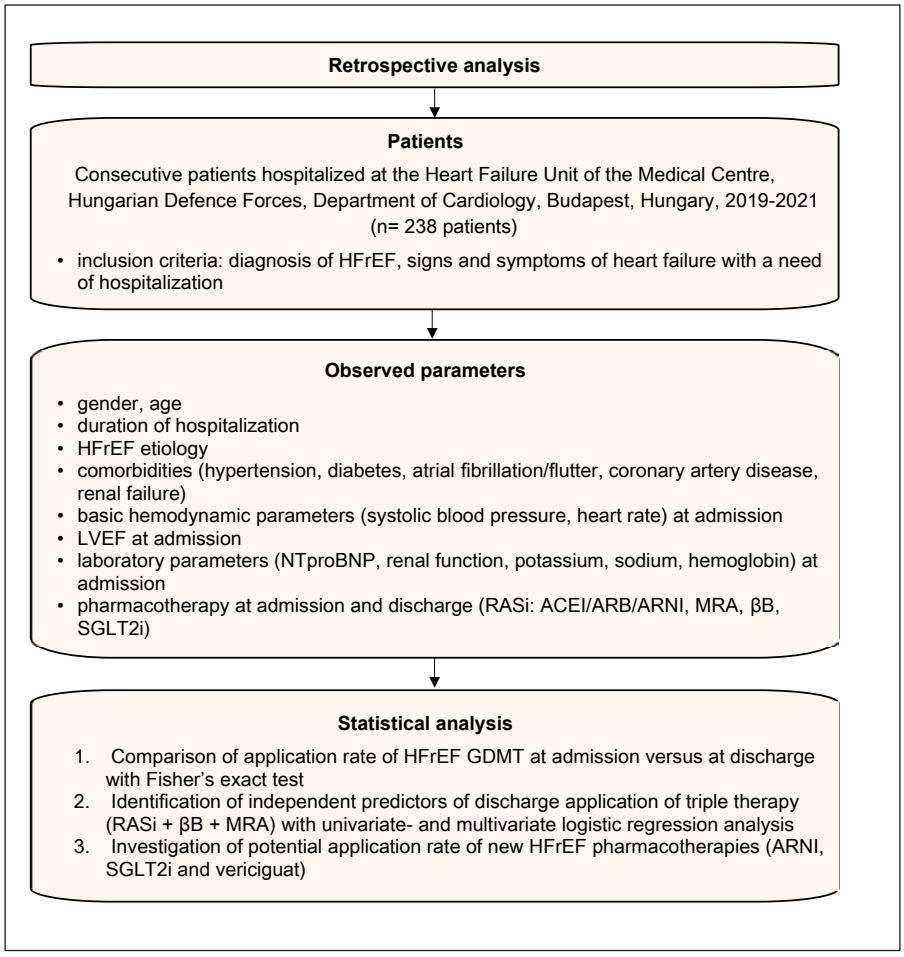
Study Population and Design

We retrospectively analyzed a consecutive, real-world HFrEF patient population hospitalized at the HF Unit of the Medical Centre, Hungarian Defence Forces, in Budapest, Hungary, between January 01, 2019 and October 31, 2021 due to signs and symptoms of HF. The study included de novo HFrEF patients who were newly diagnosed with HFrEF at hospital admission and previously diagnosed HFrEF patients who had a pre-existing diagnosis of HFrEF before hospital admission. Patients with a diagnosis of acute coronary syndrome at admission and patients who died during hospital stay were excluded. This study was approved by the local Ethical Committee (approval number KK00/144-1/2022) and was undertaken in conformity with the Helsinki Declaration. The study design is shown in Figure 1.

First, the application rate of conventional triple neurohormonal antagonist therapy – RASi (RASi: ACEI/ARB/ARNI), βB, and MRA treatment – was assessed among our patients, with a comparison of medication at admission and discharge. Even though the results of SGLT2i landmark trials (DAPA-HF [8], EMPEROR-Reduced [9]) were only published during our research period and implemented in the ESC HF Guidelines of 2021 [12], thus at the end of our data collection period, we also investigated the application rate of dapa- and empagliflozin.

Second, we evaluated the predictive value of potential factors that may influence the intrahospital applicability of triple therapy (RASi: ACEI/ARB/ARNI + βB + MRA). Demographic data (gender, age), major comorbidities (diabetes mellitus, hypertension, coronary artery disease, and atrial fibrillation), basic hemodynamic parameters (heart rate, systolic blood pressure [SBP]) at admission, laboratory parameters (estimated glomerular filtration rate [eGFR], potassium level, N-terminal pro-B-type natriuretic peptide [NTproBNP]) at admission, left ventricular ejection fraction (LVEF) at admission, length of hospitalization, dual neurohormonal antagonist medication (RASi + βB, RASi + MRA, βB + MRA) before admission and cardiac resynchronization therapy, and/or implantable cardioverter defibrillator therapy at admission were included in the univariate logistic regression analysis. Further, the significant predictive parameters of univariate logistic regression analysis were included in the multivariate logistic regression analysis. The diagnostic criteria for the assessed comorbidities are presented in online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000528505).

Third, the potential application rate of new HFrEF pharmacotherapies (ARNI, SGLT2i, vericiguat) was also investigated in our analysis. Potential application rates were determined based on the known contraindications for ARNI and SGLTi and the inclusion and exclusion criteria employed in the VICTORIA study for vericiguat. In the supplementary document of the ESC HF Guidelines of 2021, the contraindications for applying ARNI and SGLT2i treatment are clearly stated [12]. Regarding ARNI, besides anamnestic angioedema, bilateral renal artery stenosis, pregnancy/breastfeeding period, and allergic reaction, eGFR below 30 mL/min/1.73 m^2, and SBP below 90 mm Hg are contraindications for introducing sacubitril/valsartan [12]. As for SGLT2i, pregnancy/breastfeeding period, allergic reaction, eGFR below 20 mL/min/1.73 m^2, and SBP below 95 mm Hg represent the contraindications of application [12]. In this analysis, we primarily focused on the assessment of renal function and blood pressure parameters among ARNI- and SGLT2i-naive patients as these may be accurately analyzed retrospectively. The potential application rate of vericiguat was investigated based on the inclusion and exclusion criteria of the VICTORIA trial [11]



Color version available online

Fig. 1. Study design. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; βB, β blocker; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NTproBNP, N-terminal pro-B-type natriuretic peptide; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium glucose cotransporter-2 inhibitor. *$p < 0.05$.

(NYHA [New York Heart Association] 2–4 functional class, LVEF <45%, NTproBNP ≥1,000 pg/mL or ≥1,600 pg/mL in the case of atrial fibrillation, SBP ≥100 mm Hg, eGFR ≥15 mL/min/1.73 m^2).

Statistical Analysis

Data were collected from the hospital's information system and were recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, USA) in an anonymized form. Statistical analysis was undertaken using Graphpad Prism 9.3.1. (GraphPad Software LCC, USA). Based on non-Gaussian distribution, continuous variables were represented as medians and interquartile ranges, while categorical variables were expressed as counts and percentages. Statistical comparison of medication at admission and discharge was accomplished with Fisher's exact test. To identify the independent predictors of the discharge application of triple therapy, univariate and multivariate logistic regression were undertaken. Besides renal function and potassium level are well-known limiting factors of neurohormonal therapy application, literature also states that they are clearly not independent predictors [17]; thus, the potential dependency of eGFR and potassium level (as binary variable: ≤4.5 mmol/L or >4.5 mmol/L) was also investigated with Mann-Whitney test to avoid multicollinearity in multivariate regression model. The sensitivity of the multivariate model that was constructed was also analyzed. A two-sided p value <0.05 and an odds ratio (OR) value ≠ 1 were considered statistically significant.

Results

Patient Population

Among the 238 patients included in the analysis, male dominance (75%) was observed. The median age of patients was 66 (55–73) years. Ischemic origin was identified in 40%. Thirty percent of the cohort belonged to the de novo HFrEF subgroup, while 70% of them were previously diagnosed HFrEF patients. Forty-two percent of the whole patient cohort had previously been hospitalized primarily due to HF. Median duration of hospitalization was 20 (12–27) days; after discharge, 53% of the patients were followed at our HF Outpatient Clinic (shown in Table 1).

Table 1. Main characteristics of the patient population (n = 238)

	n (%)/ median (IQR)
Parameters	
Male gender, n (%)	178 (75)
Age, median (IQR), years	66 (55–73)
Duration of hospitalization, median (IQR), days	20 (12–27)
Previous hospitalization primarily due to HF, n (%)	100 (42)
Follow-up at our HFOC, n (%)	126 (53)
Time of HFrEF diagnosis	
De novo HFrEF, n (%)	71 (30)
Previously diagnosed HFrEF, n (%)	167 (70)
HF etiology	
Ischemic, n (%)	96 (40)
Nonischemic/unknown, n (%)	142 (60)
LVEF at admission, median (IQR), %	25 (20–30)
CRT/ICD therapy at admission, n (%)	66 (28)
Heart rate at admission, median (IQR), min^{-1}	88 (74–100)
SBP at admission, median (IQR), mm Hg	117 (102–134)
Comorbidities	
Diabetes, n (%)	97 (41)
Hypertension, n (%)	145 (61)
Atrial fibrillation/flutter, n (%)	114 (48)
Coronary artery disease, n (%)	96 (40)
CKD KDIGO stage (based on eGFR at admission), n (%)	
1 (eGFR ≥90 mL/min/1.73 m^2)	28 (12)
2 (eGFR = 60–89 mL/min/1.73 m^2)	79 (33)
3A (eGFR = 45–59 mL/min/1.73 m^2)	44 (19)
3B (eGFR = 30–44 mL/min/1.73 m^2)	51 (21)
4 (eGFR = 15–29 mL/min/1.73 m^2)	32 (13)
5 (eGFR <15 mL/min/1.73 m^2)	4 (2)
Laboratory parameters at admission	
Creatinine, median (IQR), µmol/L	112 (93–149)
eGFR, median (IQR), mL/min/1.73 m^2	55 (38–73)
Potassium	
Median (IQR), mmol/L	4.30 (3.94–4.70)
>4.5 mmol/L, n (%)	90 (38)
Sodium, median (IQR), mmol/L	140 (136–142)
Hemoglobin, median (IQR), g/L	131 (112–143)
NTproBNP, median (IQR), pg/mL	6,243 (2,719–12,167)
HbA1C, median (IQR), %	6.1 (5.7–6.7)

CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HFOC, Heart Failure Outpatient Clinic; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Outcomes; LVEF, left ventricular ejection fraction.

Median LVEF was 25 (20–30)%. Median NTproBNP level was significantly elevated at admission (6,243 [2,719–12,167] pg/mL). A large proportion of comorbidities (such as chronic kidney disease [CKD] Kidney Disease Improving Global Outcomes [KDIGO [18]] 3–5 stage: 55%, diabetes: 41%, hypertension: 61%, atrial fibrillation/flutter: 48%) was observed. The low LVEF, the high value of NTproBNP, and the large proportion of comorbidities clearly indicate the severity of illness of the patient population.

Comparison of the Application Rate of the Disease-Modifying Medication of HFrEF at Hospital Admission and Discharge

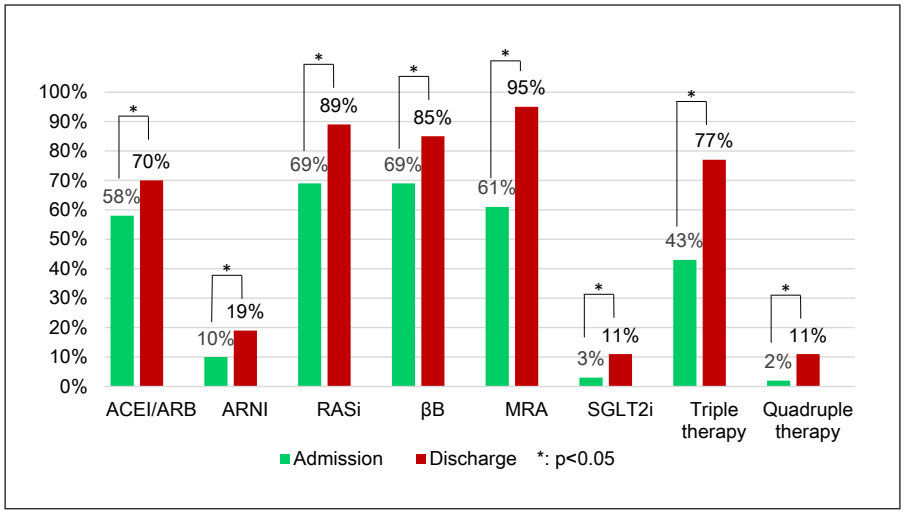
Regarding HFrEF standard medication, at admission ACEI/ARB was applied in 58%, βB in 69%, and MRA in 61% of cases. Regarding new drug treatment options, ARNI was pre-hospital implemented in 10% of the patient cohort, while 3% of the patients received SGLT2i before hospitalization. Before the index admission, 28% of the patients had already had cardiac resynchronization therapy and/or implantable cardioverter defibrillator.

During the hospitalization period, the penetration of disease-modifying medication for HFrEF increased significantly (shown in Fig. 2) as did the application of RASi (69% vs. 89% [admission vs. discharge, respectively], $p < 0.0001$, of which ACEI/ARB: 58% vs. 70%, $p = 0.0097$, and ARNI: 10% vs. 19%, $p = 0.0056$), βB (69% vs. 85%, $p < 0.0001$), and MRA (61% vs. 95%, $p < 0.0001$). The application rate of dapagliflozin and empagliflozin also increased (3% vs. 11%, $p = 0.0005$). A larger proportion of patients received triple therapy (RASi + βB + MRA) at discharge (43% vs. 77%, $p < 0.0001$). The frequency of quadruple therapy (RASi + βB + MRA + SGLT2i) also increased in comparison with medication applied at admission (2% vs. 11%) ($p < 0.0001$).

At discharge, target doses – as defined in the ESC HF Guidelines of 2021 [12] – could have been achieved in 25% of patients on RASi therapy (of which ACEI/ARB target dose was accomplished in 26% and ARNI in 22%), and target doses of βB in 27%, MRA in 69%, and SGLT2i in 93% of the cases were applied (referring only to the patients on each medication). However, only a small proportion of patients on triple therapy (8%) and on quadruple therapy (12%) received the recommended doses of all drugs.

Predictive Factors of the Discharge Application of Triple Therapy (RAS Antagonist, βB, and MRA)

Using univariate logistic regression analysis, age (OR = 0.9241, $p < 0.0001$), duration of hospitalization (OR = 0.9681, $p = 0.0011$), eGFR (OR = 1.0490, $p < 0.0001$), potassium level greater than 4.5 mmol/L (OR = 0.4483, $p = 0.0101$), NTproBNP (OR = 0.9913, $p < 0.0001$), and diabetes (OR = 0.4367, $p = 0.0076$) proved



Color version available online

Fig. 2. Changes in guideline-directed medication during hospitalization. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; βB, β blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium glucose cotransporter-2 inhibitor.

Table 2. Predictive factors of the discharge application of triple therapy with univariate logistic regression analysis

Univariate logistic regression analysis	OR	95% CI		*p* value
Age (/1 year)	0.9241[a]	0.8943	0.9513	<0.0001[a]
Female gender (yes)	0.8696	0.4459	1.7580	0.6896
Duration of hospitalization (/1 day)	0.9681[a]	0.9482	0.9871	0.0011[a]
Heart rate (/1 min^{-1})	1.0040	0.9908	1.0180	0.5497
SBP (/1 mm Hg)	1.0140	1.0000	1.0300	0.0505
eGFR (/1 mL/min/1.73 m^2)	1.0490[a]	1.0320	1.0680	<0.0001[a]
Potassium >4.5 mmol/L (yes)	0.4483[a]	0.2418	0.8258	0.0101[a]
NTproBNP (/100 pg/mL)	0.9913[a]	0.9879	0.9944	<0.0001[a]
LVEF (/1%)	1.0190	0.9755	1.0660	0.3994
Diabetes (yes)	0.4367[a]	0.2349	0.8029	0.0076[a]
Hypertension (yes)	0.5648	0.2879	1.0670	0.0792
Atrial fibrillation/flutter (yes)	0.5835	0.3144	1.0690	0.0815
Coronary artery disease (yes)	0.6909	0.3760	1.2730	0.2341
CRT/ICD at admission (yes)	0.7309	0.3839	1.4240	0.3508
Pre-hospital dual therapy (RASi + βB, RASi + MRA, βB + MRA) (yes)	0.8441	0.4322	1.7090	0.6293

βB, β blocker; CI, confidence interval; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; NTproBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; RASi, renin-angiotensin system inhibitor. [a] Significance ($p < 0.05$; OR ≠ 1).

to be predictive factors of the discharge application of triple therapy (shown in Table 2). Renal function and potassium level were not independent predictors according to the results of the Mann-Whitney test: patients with potassium levels greater than 4.5 mmol/L had significantly lower eGFR compared to those with no more than 4.5 mmol/L (46 [30–67] vs. 61 [41–79] mL/min/1.73 m^2, $p = 0.0004$). To avoid multicollinearity, only the stronger predictor eGFR was included in the multivariate logistic regression analysis, while potassium was excluded.

Analysis of these parameters with multivariate logistic regression showed that age (OR = 0.9247, $p = 0.0002$), duration of hospitalization (OR = 0.9718, $p = 0.0471$), eGFR (OR = 1.0220, $p = 0.0412$), NTproBNP (OR = 0.9946, $p = 0.0110$), and diabetes (OR = 0.3877, $p = 0.0177$) remained the independent influencing factors of the discharge application of triple therapy ($p < 0.05$) (shown in Table 3). The sensitivity of the multivariate model was 94% for the whole patient cohort, 95% for previously diagnosed HFrEF patients, and 93% for the de novo HFrEF patient subgroup, which indicated the strong predictive power of our model.

Table 3. Independent predictors of the discharge application of triple therapy identified using multivariate logistic regression analysis

Multivariate logistic regression analysis	OR	95% CI		*p* value
Age (/1 year)	0.9247[a]	0.8856	0.9613	0.0002[a]
Duration of hospitalization (/1 day)	0.9718[a]	0.9441	0.9992	0.0471[a]
eGFR (/1 mL/min/1.73 m^2)	1.0220[a]	1.0001	1.0430	0.0412[a]
NTproBNP (/100 pg/mL)	0.9946[a]	0.9904	0.9987	0.0110[a]
Diabetes (yes)	0.3877[a]	0.1732	0.8374	0.0177[a]

CI, confidence interval; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; NTproBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio. [a] Significance ($p < 0.05$; OR ≠ 1).

Applicability of New HFrEF Medication (ARNI, SGLT2i, and Vericiguat)

For seventy-nine percent of the ARNI-naive patients in our study population ($n = 193$), when considering contraindications (eGFR ≥30 mL/min/1.73 m^2: 82% [proportion of patients meeting the criteria, thus patients suitable for treatment], SBP ≥90 mm Hg: 94%), sacubitril/valsartan could have been applied. Regarding the whole patient cohort – those already on ARNI therapy *and* ARNI-naive patients – 83% would have been suitable for sacubitril/valsartan. Dapa-/empagliflozin could have been initiated in 81% of the SGLT2i-naive group ($n = 211$), based on their renal function (eGFR ≥20 mL/min/1.73 m^2: 93%) and SBP (≥95 mm Hg: 86%). As for the whole patient cohort – those already on SGLT2i therapy *and* SGLT2i-naive patients – 84% would have been suitable for empa-/dapagliflozin medication. In terms of the inclusion and exclusion criteria of the VICTORIA trial (LVEF <45%: 100%, SBP ≥100 mm Hg: 78%, eGFR ≥15 mL/min/1.73 m^2: 97%, NTproBNP ≥1,000 pg/mL and ≥1,600 pg/mL in case of atrial fibrillation: 89%, NYHA 2–4 functional class: 100%, hospitalization due to HF within 6 months: 100%), 68% of our patients would have been suitable for vericiguat therapy.

Discussion

Main Findings

Our results confirm that the application of combined neurohormonal antagonist therapy (RASi + βB + MRA) was feasible and well tolerated in the majority of our hospitalized HFrEF patients, who suffered from severe HF as verified by the laboratory, clinical parameters, and the proportion of comorbidities. The independent predictors of the discharge application of triple therapy proved to be age, duration of hospitalization, severity of kidney dysfunction, NTproBNP level at admission, and presence of diabetes mellitus. The applicability of new HFrEF medications – considering the contraindications stated in the current guidelines and based on the inclusion and exclusion criteria of randomized control trials (RCTs) – is 83% for ARNI, 84% for SGLT2i, and 68% for vericiguat.

Comparison of the Application Rate of the Disease-Modifying Medication of HFrEF at Hospital Admission and Discharge

The need for hospitalization is a marker of progressive, severe HF [19] and predicts a worse prognosis [2, 20, 21]. The significant share of readmissions indicates the relevance to healthcare of the disease, which affects 15–30% of the HF population yearly [22–24] – moreover, the proportion of those needing rehospitalization has increased recently [24].

Favorable mortality and morbidity expectations in HFrEF can only be rationally grounded on the implementation of a complex disease-modifying treatment regime recommended by international HF guidelines, as well as on the up-titration of the respective life-saving drugs to their target doses or the tolerated maximal doses [25, 26]. For these reasons, we must strive to optimize pharmacotherapy in this high-risk, hospitalized HFrEF population because in-hospital-adjusted medical therapy strongly impacts long-term pharmacotherapy [27, 28].

Our results show that a significant increase in the use of neurohormonal antagonists and triple therapy can be achieved during hospitalization. Few studies have thus far investigated the success of intrahospital therapy optimization and its limiting factors in a consecutive HFrEF population with worsening HF. Although objective comparison can be hard due to the different inclusion criteria of trials and different patient populations [7–9, 11, 13, 14, 23, 29–35] (shown in online suppl. Table S2),

our results indicate that the proportion of patients on neurohormonal antagonist therapy was comparable or even larger than verified in the related analyses of national and international registries and epidemiological studies [23, 29]. The 77% application rate of triple therapy exceeded that identified in randomized controlled trials that evaluated the data of patients hospitalized for worsening HF (VICTORIA trial: 66.1% [11], GALACTIC-HF: 60.7% [32]), as well as in registries (CHAMP-HF Registry: 22.1% [13], IMPLEMENT-HF Pilot Study: 26% [35], VICTORIA Registry: 28.4% [31]) and epidemiological studies (Humana Research Database: 29% [14]). As our analysis shows, the share of patients on target doses of neurohormonal antagonist medication is comparable with that identified in landmark trials and registries [13, 36–38].

The recently published VICTORIA Registry – with a comparable study structure to ours – has investigated intrahospital therapy optimization and its limiting factors in a HFrEF population with worsening HF [31]. Similarly to our results, the VICTORIA Registry showed an increase in the proportion of patients receiving neurohormonal antagonists and triple therapy during hospitalization, but a smaller share of patients received RASi (66.8% vs. 89%, VICTORIA Registry vs. our results), βB (75.1% vs. 85%), and MRA (44.9% vs. 95%) treatment as well as triple therapy (28.4% vs. 77%) at discharge than in our study. As for the target doses, the proportion of patients on optimal medication in our study exceeded the referring results of the VICTORIA Registry (ACEI/ARB: 12.6% vs. 26%; ARNI: 19.9% vs. 22%; βB: 17.5% vs. 27%; MRA: 71.2 vs. 69%), which thus achieved a significantly larger proportion of target doses of triple therapy (1.5% vs. 8%).

The incidence of comorbidities may not only be a marker of the vulnerability of HF patients that has the potential to trigger HF progression [25] but also requires a more complex pharmacotherapy [39] and may be a significant limiting factor of disease-modifying drug-therapy initiation and up-titration to target doses. The proportion of comorbidities in our patient cohort regarding diabetes, hypertension, atrial fibrillation/flutter, and coronary artery disease was comparable to that identified in data from the European ESC-HF-LT Registry [23] and the national Hungarian HF Registry [29], as well as randomized clinical trials [7–9, 11, 32, 34] (shown in online suppl. Table S3). The greater prevalence of significant chronic renal failure verified in our analysis may represent the vulnerability of the cohort and explain the less frequent use of RASi and MRA at hospital admission [40]. It must also be highlighted that most large, randomized, controlled HF trials that have examined the efficacy of different new drugs on the prognosis of HF mainly included pre-selected, stable, chronic HFrEF patients. In contrast, we assessed the application rate of HFrEF GDMT in a consecutive, previously unselected, real-world population hospitalized over a period of 3 years at the HF unit of our tertiary cardiac center and admitted for HF.

The results of our study may indicate that in this group of hospitalized patients suffering from severe HFrEF with severely decreased left ventricular systolic dysfunction, numerous significant comorbidities, highly elevated NT-proBNP, and a prevalence of previous hospitalization, neurohormonal antagonist therapy can be achieved in a large proportion; moreover, the application of target doses is also feasible.

Predictive Factors of the Discharge Application of Triple Therapy (RAS Antagonist, βB, and MRA)

The discharge application of triple therapy according to our analysis was influenced by duration of hospitalization, age, renal function, diabetes mellitus, and the level of NTproBNP at admission. Longer hospital stays, older age, more severely impaired kidney function, presence of diabetes mellitus, and higher NTproBNP level at admission predicted less likelihood of the discharge application of triple therapy.

ESC HF Guidelines [12] suggest discharging patients only after complete decongestion as well as the application of all disease-modifying medications. The more serious a patient's condition is, the longer it takes to meet this recommendation and the less likely it is to succeed. Average duration of hospitalization for HF is approximately 6–7 days in the USA and 8–9 days in European countries [41]; in contrast, our patients spent a median 20 days at our HF unit. Longer hospital stays may facilitate the watchful implementation of GDMT as recommended in the ESC HF Guidelines of 2021, even among patients with a high burden of significant comorbidities in severe clinical condition. However, in the most severe cases, triple therapy is often not achievable or is achievable only when using a slower and more careful titration regime, resulting in significantly longer hospitalization time. This may explain the inverse correlation – as confirmed by our multivariate regression analysis – between longer hospital stays and the applicability of triple therapy.

CKD is a prevalent comorbidity in HFrEF and represents a strong independent risk factor of poor outcome [42–44]. Further, CKD often makes it difficult to

implement GDMT. CKD is one of the most frequent reasons why physicians do not initiate or titrate or even discontinue or reduce the dosages of neurohormonal antagonists for patients with HFrEF. However, even patients with the worst kidney function benefit from neurohormonal antagonist therapy, and one should not discount the favorable effect on the slope of eGFR of ARNI [45] and SGLT2i [46, 47]. Nevertheless, it is a well-established fact that CKD not only makes the introduction of neurohormonal antagonists – especially RASi – difficult but in many cases impossible. In our sample, worsening renal function was associated with lower rates of GDMT use, although implemented complex GDMT was significantly more favorable than found in the data of the international HF registries [48, 49]. Several previous studies have investigated the independent influencing factors of therapy optimization in HFrEF. Similarly to our results, the CHAMP-HF Registry [13], which assessed the data of an outpatient HFrEF cohort, verified renal failure as the independent predictor of the application of neurohormonal antagonists (RASi, βB, MRA). Additionally, in the BIOSTAT CHF registry [37], low eGFR was found to be an independent predictor of a lower recommended ACEI/ARB dose. In the VICTORIA Registry [31], less severe kidney dysfunction facilitated the initiation/up-titration of ACEI/ARB and MRA therapy.

Diabetes mellitus is estimated to occur in approximately 40% of patients with acute HF and 25% of patients with chronic HF [50]. Diabetes mellitus has a strong two-way interaction with CKD: data suggest that 16% of HF patients have comorbid diabetes mellitus and CKD [51]. The presence of diabetes mellitus can lead to worsening kidney function, lessening the tolerability of HFrEF neurohormonal antagonist medication, which partly explains the strong impact of diabetes on the application of triple therapy in our patient cohort. The results of a recently published study also reveal the significantly lower level of application of RASis in a large real-world patient cohort of diabetic HF patients [52].

Even though older persons have been underrepresented in RCTs [53–55], the favorable effect of disease-modifying medication among them has already been proven [56–59]. However, it is well known that in everyday clinical practice the initiation and optimization of GDMT in the aging population lags behind that of younger people. In concordance with our results, in the CHECK-HF Registry [60], CHAMP-HF Registry [13], and BIOSTAT-CHF Registry [37, 61] age was recognized as a prognostic factor per se of GDMT application, notwithstanding its relevance in terms of determining adherence with GDMT.

In our analysis, the median NTproBNP level at admission notably exceeded the median values presented in the landmark randomized controlled clinical trials [7–9] and was even higher than that reported in studies that assessed patients hospitalized for acute decompensation [11, 30, 32, 34]. In patients with a severe clinical condition characterized by a high NTproBNP level, higher rates of hypotension and renal impairment make GDMT use difficult. This may explain the correlation observed in our study between a higher NTproBNP level and a lower rate of the discharge application of triple therapy.

Applicability of New HFrEF Medication (ARNI, SGLT2i, and Vericiguat)

HFrEF shows continuous progression, despite optimized medical treatment. We may only hope for the best outcome if we are engaged in applying the whole spectrum of available pharmacotherapy. For these reasons, recent studies about SGLT2i, ARNI, and vericiguat are of outstanding importance as completing conventional therapy with these new medications that target new pathways has been shown to significantly improve the life expectancy of HFrEF patients.

Thus, in our analysis we evaluated the potential applicability of the new HFrEF pharmacological agents such as ARNI, SGLT2i, and vericiguat. The low application ratio of ARNI and SGLT2 inhibitors in our study might have a multifactorial origin. It may partly be due to local Hungarian reimbursement conditions; furthermore, the first-line application of dapa- and empagliflozin was only implemented – based on the results of DAPA-HF [8] and EMPEROR-Reduced [9] studies – in international HF guidelines [12, 62] after our study was designed. According to the current ESC HF Guidelines and the related supplementary document [12], among our patients, ARNI and SGLT2i medication could have been applied in 83–84% of cases. Literature estimates the potential applicability of SGLT2i in chronic HFrEF population as wide [63–65]. In the analysis of the SwedeHF Registry, the SGLT2i-suitable patient ratio was 35%, 61%, and 80% for dapagliflozin and 31%, 55%, and 81% for empagliflozin depending on the criteria (trial, pragmatic, or label scenarios, respectively) [63]. Regarding the potential application rate of ARNI, this also varies widely depending on the cohort and the criteria that are applied. In an outpatient cohort, according to the PARADIGM HF inclusion and exclusion criteria, 11–13% of the examined patients would have been suitable for ARNI [66]. Similarly, according to the analysis of Backelin et al. [67] among 1,355 hospitalized HF patients 20% would have been suitable

for ARNI according to the RCT criteria. In contrast to the results of previous studies that assessed eligibility for ARNI treatment based on the inclusion and exclusion criteria of the PARADIGM HF trial, in our analysis the contraindications for ARNI implementation of the 2021 ESC HF Guidelines were taken into account. The relatively few factors representing contraindications for the initiation of these drugs in our real-world cohort call attention to the need for the more conscious implementation of ARNI and SGLT2i treatment in daily clinical practice.

Although vericiguat is not yet available in most countries in daily clinical practice, it could be a potentially effective therapeutic option for patients presenting with worsening HF in spite of optimal medical therapy. Our results indicated that 68% of our cohort would have been eligible for vericiguat therapy based on the inclusion and exclusion criteria of the VICTORIA trial [11], which finding correlates with the Korean Acute HF Registry's determination of 58% applicability in that population [68].

Conclusions

HF is still a major public health problem which significantly impacts the life expectancy of affected patients. Their prognosis can be improved through the implementation and successful optimization of a complex disease-modifying drug regime, although in everyday practice this is not always achievable. According to our analysis, the initiation and optimization of this life-saving drug regime are possible even in a hospitalized HFrEF patient cohort despite the major burden of significant comorbidities and clinical severity of the real-life population.

Our analysis found that the implementation of GDMT was influenced by several factors. Longer hospital stays, older age, more severely impaired kidney function, presence of diabetes mellitus, and higher NTproBNP level at admission predicted less likelihood of the discharge application of triple therapy.

Our findings show that the majority of HFrEF patients are suitable for new pharmacotherapies (SGLT2i, ARNI, and vericiguat) that can affect significantly the prognosis of the disease. Accordingly, awareness of the need for their initiation in daily clinical practice must be raised.

Limitations

Although our single-center analysis represents a real-world HF population with a high comorbidity burden, it has some limitations. Our single-center patient population consisted of only Caucasians. Accordingly, the results of the study may not apply to patients outside this group.

An additional limitation regarding the use of SGLT2i in everyday clinical practice is that the data collection process for our patient cohort started before the publication of the results of DAPA-HF and EMPEROR-Reduced studies. Since then, there have been changes in the guideline recommendations (in the ESC HF Guidelines of 2021) regarding the pharmacological therapy of HFrEF, which could have modified the application ratio of SGLT2is in relation to these clinical circumstances. Moreover, SGLT2i application among nondiabetic HF patients still represents a major limitation in everyday clinical practice as SGLT2is are only reimbursed for diabetic patients in Hungary. The use of sacubitril/valsartan may also be affected by reimbursement conditions in Hungary as the latter is only available to HFrEF patients if they have been hospitalized for HF at least twice, have been on optimal HFrEF treatment for at least 1 year, have elevated NTproBNP levels, are defined as NYHA functional class 2-3, and have LVEF below 35%.

Acknowledgment

We would like to thank Simon John Milton for his help with language-related questions.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Research Ethics Committee of Medical Centre, Hungarian Defence Forces, approval number KK00/144-1/2022 in accordance with the World Medical Association Declaration of Helsinki. For our observational study, no written informed consent was required as our research did not influence the professional medical care of the patients, required no intervention, and contained only retrospective data collection in an anonymized form, which was approved by the Institutional Research Ethics Committee of Medical Centre, Hungarian Defence Forces, approval number KK00/144-1/2022.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors received no funding sources.

Author Contributions

Fanni Bánfi-Bacsárdi conceived and designed the study, performed data collection, analyzed statistically the data, designed data interpretation, and drafted the manuscript. Balázs Muk conceived and designed the study, performed data collection, revised statistical analysis, revised critically, and corrected the manuscript. Dávid Pilecky, Gábor Zoltán Duray, and Róbert Gábor Kiss contributed to the critical revision and correction of the manuscript. Noémi Nyolczas contributed to data interpretation, revised critically, and corrected the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary materials. Further inquiries can be directed to the corresponding author.

References

1 Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020;22(8):1342–56.
2 Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail. 2014;1(1):4–25.
3 Mamas MA, Sperrin M, Watson MC, Coutts A, Wilde K, Burton C, et al. Do patients have worse outcomes in heart failure than in cancer? A primary care-based cohort study with 10-year follow-up in Scotland. Eur J Heart Fail. 2017;19(9):1095–104.
4 Blumer V, Mentz RJ, Sun JL, Butler J, Metra M, Voors AA, et al. Prognostic role of prior heart failure hospitalization among patients hospitalized for worsening chronic heart failure. Circ Heart Fail. 2021;14(4):e007871.
5 Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola VP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19(12):1574–85.
6 Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure. J Card Fail. 2021;27(4):387–413.
7 McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.
8 McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.
9 Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24.
10 Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819–29.
11 Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med. 2020;382(20):1883–93.
12 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
13 Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. J Am Coll Cardiol. 2018;72(4):351–66.
14 Wirtz HS, Sheer R, Honarpour N, Casebeer AW, Simmons JD, Kurtz CE, et al. Real-world analysis of guideline-based therapy after hospitalization for heart failure. J Am Heart Assoc. 2020;9(16):e015042.
15 Bress AP, King JB. Optimizing medical therapy in chronic worsening HFrEF: a long way to go. J Am Coll Cardiol. 2019;73(8):945–7.
16 Mentz RJ, Lautsch D, Pulungan Z, Kim S, Hilkert R, Teigland C, et al. Medication trajectory and treatment patterns in medicare patients with heart failure and reduced ejection fraction. J Card Fail. 2022;28(8):1349–54.
17 Gumz ML, Rabinowitz L, Wingo CS. An integrated view of potassium homeostasis. N Engl J Med. 2015;373(1):60–72.
18 Kidney Disease: Improving Global Outcome. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease; 2013.
19 Kassis-George H, Verlinden NJ, Fu S, Kanwar M. Vericiguat in heart failure with a reduced ejection fraction: patient selection and special considerations. Ther Clin Risk Manag. 2022;18:315–22.
20 Zhang Y, Zhang J, Butler J, Yang X, Xie P, Guo D, et al. Contemporary epidemiology, management, and outcomes of patients hospitalized for heart failure in China: results from the China heart failure (China-HF) registry. J Card Fail. 2017;23(12):868–75.
21 Greene SJ, Fonarow GC, Butler J. Risk profiles in heart failure: baseline, residual, worsening, and advanced heart failure risk. Circ Heart Fail. 2020;13(6):e007132.
22 Khan MS, Sreenivasan J, Lateef N, Abougergi MS, Greene SJ, Ahmad T, et al. Trends in 30- and 90-day readmission rates for heart failure. Circ Heart Fail. 2021;14(4):e008335.
23 Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, et al. European society of Cardiology heart failure long-term registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. Eur J Heart Fail. 2016;18(6):613–25.
24 Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. Nat Rev Cardiol. 2015;12(4):220–9.
25 Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. J Am Coll Cardiol. 2019;73(8):935–44.
26 Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. JACC Heart Fail. 2022;10(2):73–84.
27 Gattis WA, O'Connor CM. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure. Am J Cardiol. 2004;93(9a):74b–6b.
28 Butler J, Arbogast PG, Daugherty J, Jain MK, Ray WA, Griffin MR. Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. J Am Coll Cardiol. 2004;43(11):2036–43.
29 Nyolczas N, Heltai K, Borbély A, Habon T, Járai Z, Sziliczei E, et al. [Hungarian heart failure registry 2015-2016. Preliminary results]. Orv Hetil. 2017;158(3):94–100.
30 Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117–28.
31 Greene SJ, Ezekowitz JA, Anstrom KJ, Demyanenko V, Givertz MM, Piña IL, et al. Medical therapy during hospitalization for heart failure with reduced ejection fraction: the VICTORIA registry. J Card Fail. 2022;28(7):1063–77.
32 Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med. 2021;384(2):105–16.

33 Tran RH, Aldemerdash A, Chang P, Sueta CA, Kaufman B, Asafu-Adjei J, et al. Guideline-directed medical therapy and survival following hospitalization in patients with heart failure. Pharmacotherapy. 2018;38(4):406–16.
34 Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022;28(3):568–74.
35 Bhatt AS, Varshney AS, Nekoui M, Moscone A, Cunningham JW, Jering KS, et al. Virtual optimization of guideline-directed medical therapy in hospitalized patients with heart failure with reduced ejection fraction: the IMPLEMENT-HF pilot study. Eur J Heart Fail. 2021;23(7):1191–201.
36 Investigators CII, Committees; The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9–13.
37 Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J. 2017;38(24):1883–90.
38 Bress AP, King JB, Brixner D, Kielhorn A, Patel HK, Maya J, et al. Pharmacotherapy treatment patterns, outcomes, and health resource utilization among patients with heart failure with reduced ejection fraction at a U.S. Academic medical center. Pharmacotherapy. 2016;36(2):174–86.
39 Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet. 2018;391(10120):572–80.
40 Mullens W, Martens P, Testani JM, Tang WHW, Skouri H, Verbrugge FH, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2022;24(4):603–19.
41 Cowie MR, Anker SD, Cleland JGF, Felker GM, Filippatos G, Jaarsma T, et al. Improving care for patients with acute heart failure: before, during and after hospitalization. ESC Heart Fail. 2014;1(2):110–45.
42 Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJV, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113(5):671–8.
43 Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35(7):455–69.
44 Lofman I, Szummer K, Dahlstrom U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail. 2017;19(12):1606–14.
45 Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail. 2018;6(6):489–98.
46 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
47 Wanner C, Inzucchi SE, Lachin JM, Fitchett D, Von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323–34.
48 Chen YL, Hang CL, Su CH, Wu PJ, Chen HC, Fang HY, et al. Feature and impact of guideline-directed medication prescriptions for heart failure with reduced ejection fraction accompanied by chronic kidney disease. Int J Med Sci. 2021;18(12):2570–80.
49 Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, et al. Kidney function and outcomes in patients hospitalized with heart failure. J Am Coll Cardiol. 2021;78(4):330–43.
50 Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. Card Fail Rev. 2017;3(1):52–5.
51 Lawson CA, Seidu S, Zaccardi F, McCann G, Kadam UT, Davies MJ, et al. Outcome trends in people with heart failure, type 2 diabetes mellitus and chronic kidney disease in the UK over twenty years. EClinicalMedicine. 2021;32:100739.
52 Radhoe SP, Veenis JF, Linssen GCM, van der Lee C, Eurlings LWM, Kragten H, et al. Diabetes and treatment of chronic heart failure in a large real-world heart failure population. ESC Heart Fail. 2022;9(1):353–62.
53 Milinković I, Polovina M, Coats AJ, Rosano GM, Seferović PM. Medical treatment of heart failure with reduced ejection fraction in the elderly. Card Fail Rev. 2022;8:e17.
54 Stolfo D, Sinagra G, Savarese G. Evidence-based therapy in older patients with heart failure with reduced ejection fraction. Card Fail Rev. 2022;8:e16.
55 Seo WW, Park JJ, Park HA, Cho HJ, Lee HY, Kim KH, et al. Guideline-directed medical therapy in elderly patients with heart failure with reduced ejection fraction: a cohort study. BMJ Open. 2020;10(2):e030514.
56 Chiu CH, Lin TY. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;354(9194):2001–2.
57 Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215–25.
58 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709–17.
59 Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation. 2020;141(2):100–11.
60 Brunner-La Rocca HP, Linssen GC, Smeele FJ, van Drimmelen AA, Schaafsma HJ, Westendorp PH, et al. Contemporary drug treatment of chronic heart failure with reduced ejection fraction: the CHECK-HF registry. JACC Heart Fail. 2019;7(1):13–21.
61 Mordi IR, Ouwerkerk W, Anker SD, Cleland JG, Dickstein K, Metra M, et al. Heart failure treatment up-titration and outcome and age: an analysis of BIOSTAT-CHF. Eur J Heart Fail. 2021;23(3):436–44.
62 Writing Committee M, Members AAJC. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Card Fail. 2022;28(5):e1–67.
63 Thorvaldsen T, Ferrannini G, Mellbin L, Benson L, Cosentino F, McMurray JJV, et al. Eligibility for dapagliflozin and empagliflozin in a real-world heart failure population. J Card Fail. 2022;28(7):1050–62.
64 Maltes S, Cunha GJL, Rocha BML, Presume J, Guerreiro R, Henriques C, et al. Dapagliflozin in a real-world chronic heart failure population: how many are actually eligible? Cardiology. 2021;146(2):201–6.
65 Angelini G, Albanese M, Ursi R, Lisi F, Bellino MC, Amato L, et al. Eligibility of outpatients with chronic heart failure for sodium-glucose co-transporter-2 inhibitors. ESC Heart Fail. 2021;8(4):2951–8.
66 Muk B, Szabo B, Dekany M, Bogyi P, Vagany D, Majoros Z, et al. The effect of treatment optimization on the suitability of ARNI among patients followed at a heart failure outpatient clinic. Eur Heart J. 2015;36(Suppl 1):509–847.
67 Nordberg Backelin C, Fu M, Ljungman C. Early experience of Sacubitril: Valsartan in heart failure with reduced ejection fraction in real-world clinical setting. ESC Heart Fail. 2020;7(3):1049–55.
68 Oh J, Lee CJ, Park JJ, Lee SE, Kim MS, Cho HJ, et al. Real-world eligibility for vericiguat in decompensated heart failure with reduced ejection fraction. ESC Heart Fail. 2022;9(2):1492–5.