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Temporal trends in guideline-recommended medical therapy after an acute heart failure decompensation event: an observational analysis from Generator Heart Failure DataMart

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ABSTRACT

Objectives To evaluate the trend of prescription of the four foundational therapies, and their impact on 30-day urgent re-admissions and all-cause death in patients with heart failure and reduced ejection fraction (HFrEF) following an acute decompensation event.

Design Retrospective.

Setting One tertiary referral centre.

Participants 999 consecutively patients admitted with a primary diagnosis of HFrEF between January 2020 and June 2023 were identified through a validated, high-performance technology infrastructure based on artificial intelligence. The entire cohort was divided into three time periods based on two time points: September 2021 (ie, the release of the latest European guidelines) and January 2022 (ie, reimbursement for sodium-glucose cotransporter 2 (SGLT2) inhibitors).

Primary and secondary outcome measures Trends and predictors of the prescription of each of the four foundational therapies and of the composite of all-cause death and rehospitalisation for urgent causes at 30 days.

Results Among the 999 included patients, β-blockers were prescribed in 93% of patients, ACE inhibitor (ACEi)/angiotensin receptor blocker (ARB)/angiotensin–neprilysin receptor inhibitor (ARNi) in 73%, mineralocorticoid receptor antagonist in 30% and SGLT2 inhibitors in 18%. Over time, an increase in the prescription rate occurred only for SGLT2 inhibitors (3% vs 10% vs 32%, p<0.001), whereas the rate of the composite of all-cause death and rehospitalisation for urgent causes at 30 days remained stable (9.9% vs 10.3% vs 8.4%; p=ns). In multivariate analysis, the use of ACEi/ARB/ARNi was associated with a lower risk of 30-day all-cause death and urgent rehospitalisation (adjusted OR 0.38; 95% CI 0.24 to 0.59; p<0.01). Conversely, the prescription of furosemide at discharge (adjusted OR 2.25; 95% CI 95% 1.29 to 3.94; p<0.01) and a previous genitourinary infection (adjusted OR 4.02; 95% CI 1.67 to 9.68; p<0.01) were associated with higher risk of 30-day all-cause death and urgent rehospitalisation.

Conclusions In our study, early adoption of guideline-recommended medical therapy is still limited, with a significant rise in SGLT2i prescriptions after January 2022 and a lower risk of the composite of all-cause death and urgent readmissions at 30 days restricted to the use of ACEi/ARB/ARNi.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main strength of the current work is the inclusion of a large, unselected and real-world cohort of patients with heart failure (HF) and reduced ejection fraction (EF), comprising also categories often excluded from large randomised controlled trials (ie, elderly and multicomorbid patients).
⇒ As first limitation, we report the experience of a single tertiary referral centre, introducing a selection bias.
⇒ As second limitation, we were unable to assess the admission to other centres within 30 days of discharge.
⇒ Given the observational and retrospective design of the study, the influence of unknown factors cannot be excluded despite adjustment for known confounders.
⇒ Diagnosis is based on International Classification of Diseases-9 codes, which do not have 100% specificity and sensitivity for detecting HF, and the exclusive inclusion of patients with a documented EF value may have further reduced diagnostic sensitivity.

INTRODUCTION

According to registry data mainly from Western countries, up to 50% of patients with heart failure (HF) exhibited reduced ejection fraction (EF).[1] In this subgroup of patients,

various pharmacological strategies have been shown to improve prognosis and quality of life, quickly reshaping the therapeutic landscape. These findings have been acknowledged by the current guidelines, indicating as a first-line pharmacological regimen a quadruple therapy based on an ACE inhibitor (ACEi), an angiotensin receptor blocker (ARB) or an angiotensin–neprilysin receptor inhibitor (ARNi), a β-blocker, a mineralocorticoid receptor antagonist (MRA) and a sodium-glucose cotransporter 2 inhibitor (SGLT2i) (class of recommendation I, level of evidence A).[2] However, in daily clinical practice, the implementation of guideline-recommended medical therapy (GRMT) is often suboptimal, especially for patients hospitalised after a decompensation event.[3] Most of the landmark randomised controlled trials (RCTs) have been conducted in the outpatient setting, while data on in-hospital medication management of patients with HF and reduced EF (HFrEF) are relatively modest, explaining, at least in part, the reluctance to implement the four foundational therapies in the in-hospital setting or at discharge. Nevertheless, accumulating data suggest that a fast-track strategy of implementation might be beneficial, since the clinical characteristics rather than the site of initiation may determine the effectiveness of the therapy.[2–4] Of note, the immediate post-discharge period is the time when more cardiovascular adverse events occur and the benefits of early implementation of GRMT could be more relevant.[5] To date, the decision whether to prescribe GRMT in the hospital setting is left at the discretion of the treating physician, who considers the patient's baseline characteristics, the current recommendations, the drug reimbursement and the predictable adherence to therapy. The feasibility and the effective prescription of the four foundational therapies, as well as their relative impact on early cardiovascular events are not fully described in a real-world scenario. In this observational cohort study, including patients with a primary diagnosis of HFrEF at hospital discharge, we aimed to evaluate the effective prescription of GRMT, the predictors of prescription and their association with the composite of all-cause death and urgent readmissions within 30 days from discharge.

METHODS

Data extraction, conversion and validation: Gemelli Generator HF DataMart framework

Methods have been published and described previously elsewhere.[3 6] Briefly, 'Gemelli Generator HF DataMart' is an advanced and high-performance technological infrastructure, aimed at collecting clinical, laboratory, imaging and on-site contact data of HF patients treated at Policlinico A. Gemelli, starting from 2019, in accordance with the CODE-electronic health record framework.[6 7] In the present observational study, HF patients are selected based on diagnosis codes listed in online supplemental table S1. Using a similar methodology, further data marts have been created for other diseases. Three physicians (RL, DAP and GC) manually validated the data extracted for the entire cohort of patients to guarantee their accuracy.

Sample population

For the current analysis, we focused on consecutive HFrEF patients discharged between January 2020 and June 2023, identified through the code 428.*, 402.*, 410.*, 411.*, 413.*, 414.*, 424.* and 427.* of the International Classification of Diseases, Ninth Revision (ICD-9), and at least one echocardiogram showing an EF of less than 40% (online supplemental table S1). In the case of multiple records, we selected the first record with HF as the primary diagnosis and evaluated the management approach used during the first event. Patients who died during hospitalisation were excluded.

Variables

From the Gemelli Generator HF Data Mart, a total of 30 variables were selected, including administrative and structured clinical data. Contraindications and cautions to ACEi/ARB/ARNi, β-blockers, MRA and SGLT2i were defined according to the 2021 ESC Guidelines on HF (online supplemental table S2). Comorbidities were assigned according to the latest guidelines and, further, confirmed and validated according to Joint Commission International standards. A detailed description of the variables selected and used in the study is provided in online supplemental table S3.

We identified two time points (ie, September 2021 and January 2022) corresponding, respectively, to the entry into force of the latest ESC HF guidelines and the redeemability of SGLT2i in Italy, thus obtaining three subgroups of patients (ie, those discharged before September 2021, between September 2021 and January 2022, and after January 2022), to assess the trends of four foundational therapies prescriptions and the composite of all-cause death and urgent readmission at 30 days throughout the three-time intervals.

Statistical analysis

Continuous variables were reported as median and IQR, and categorical variables were reported as counts and proportions (percentages). Baseline characteristics were assessed in the entire cohort and compared using the Kruskal-Wallis test for continuous variables and Pearson's χ^2 test for categorical variables. Unadjusted and adjusted ORs with 95% CIs were calculated by fitting univariate and multivariate logistic regression models, respectively, to assess the predictors of the prescription of each foundational therapy, and of the composite of all-cause death and urgent readmissions for all causes at 30 days. Urgent readmissions were defined as those that are unplanned and result in access to the emergency department. In multivariate models, missing data were handled by chained equation multiple imputation. Variables included in the multiple imputation model were laboratory values given their lower missing rates. Multivariate

analysis included time of prescription (before September 2021, between September 2021 and January 2022, and after January 2022), demographics (age and sex), clinical variables (heart rate), laboratory values (N-terminal pro-B-type natriuretic peptide (NT-proBNP), estimated glomerular filtration rate (eGFR), potassium and haemoglobin), concomitant medications (ie, diuretics and, specifically, furosemide), comorbidities (diabetes, pulmonary disease, malignant disease, hypertension and hepatic disease), cautions and contraindications (ie, hyperkalaemia, significant renal dysfunction, hypotension, genitourinary infection and heart block). Moreover, we applied feature selection based on the backward feature elimination method, maintaining only significant variables in the final models. Statistical analysis was performed using Python V.3.6.8 with main packages: *pandas* for data processing, *scipy* for statistical tests, *statsmodels* for modelling, *matplotlib, scikit-learn* for data imputation and *zepid* for reporting. In addition, we used SAS for extract, transform, load data extraction and text mining pipelines. A p<0.05 was considered statistically significant.

Sensitivity analyses

We performed two sensitivity analyses: (1) focusing on the prescription of ARNi only, we specifically evaluated its prescription trend over time, and its predictors of prescription apart from ACEi and ARB and (2) since empagliflozin became reimbursable a few months later than dapagliflozin (ie, June 2022), we specifically evaluated the rate and predictor of SGLT2i prescription in patients discharged after June 2022.

RESULTS

Considering the period from January 2020 to June 2023 as the baseline period for the scope of this observational study, the Gemelli Generator HF Data Mart included 12 087 patients, of whom 999 with a diagnosis of HFrEF confirmed at admission based on echocardiographic assessment of EF (figure 1).

The baseline characteristics of the entire population are shown in online supplemental table S4. The median age of the overall population was 71 years (IQR, 62–79 years), and 77.9% of patients were men. Missing rates for baseline characteristics are reported per variable in online supplemental table S4, whereas missing values for contraindications/cautions are reported in online supplemental table S5.

Rate of prescription at discharge

At discharge, 93% of patients received a β-blocker, 73% were prescribed an ACEi/ARB/ARNi, of which 64.6% were receiving ARNi, 30% an MRA and 18% an SGLT2 inhibitor. From a temporal perspective, 416 (41.6%) patients were discharged before September 2021, 97 (9.7%) between September 2021 and January 2022, and 486 (48.7%) after January 2022.

Temporal trends per pillar type and pillar number

The prescription trend of the four foundational therapies at discharge, classified as both number and type, is shown in figures 2 and 3. The prescription rate remained stable in the three interval time for β-blockers (92.5% vs 95.5% vs 92.6%, p=ns) and for MRAs (33.4% vs 30.9% vs 27.8%, p=ns), while a gradual increase in the prescription of ACEi/ARB/ARNis (69.2% vs 72.2% vs 76.7%, p=0.039) and more remarkably of SGLT2 inhibitors occurred both after September 2021 (10.3%) and January 2022 (31.9%), compared with before September 2021 (3.1%) (p<0.01) (table 1).

The prescription patterns according to the combinations used and the type of drug within the three-interval time are shown in table 2.

Considering ARNi alone, there has been a significant increase in their prescription, becoming preferred to ACEi/ARBs over time (figure 2).

Missed prescription rate for each pillar

ACEi/ARB/ARNi

It could have been, but was not, prescribed to 16.6% of patients (table 1). Considering the three-time intervals separately, the missed prescriptions were 19.2%, 14.4% and 14.8%, respectively (table 1).

Beta-blocker

It could have been, but was not, prescribed to 5.7% of patients (table 1). Considering the three-time intervals separately, the missed prescriptions were 6%, 2.1% and 6.2%, respectively (table 1).

Mineralocorticoid receptor antagonist

It could have been, but was not, prescribed to 61.6% of patients (table 1). Considering the three-time intervals separately, the missed prescriptions were 58.2%, 59.8% and 64.8%, respectively (table 1).

Sodium-glucose cotransporter 2 inhibitor

It could have been, but was not, prescribed to 63.8% of patients (table 1). Considering the three-time intervals separately, the missed prescriptions were 79.1%, 55.7% and 52.3%, respectively (table 1).

Predictors of drugs' prescription at discharge per pillar

The predictors of prescription of each pillar at multivariate analysis are shown in figure 4. The multivariate analysis was not performed for β-blockers, as they were being prescribed to more than 90% of patients.

ACEi/ARB/ARNi

'Significant renal dysfunction' (adjusted OR 0.12, 95% CI (0.07 to 0.22)), 'hypotension' (adjusted OR 0.35; 95% CI (0.22 to 0.56)), 'hyperkalaemia' (adjusted OR 0.36; 95% CI (0.16 to 0.82)) and increasing 'age' (adjusted OR 0.96; 95% CI (0.95 to 0.98)) emerged as independent negative predictors of prescription, while 'diabetes' (adjusted OR 1.52; 95% CI (1.11 to 2.07)) and higher level of 'haemoglobin' (adjusted OR 1.13; 95% CI (1.05

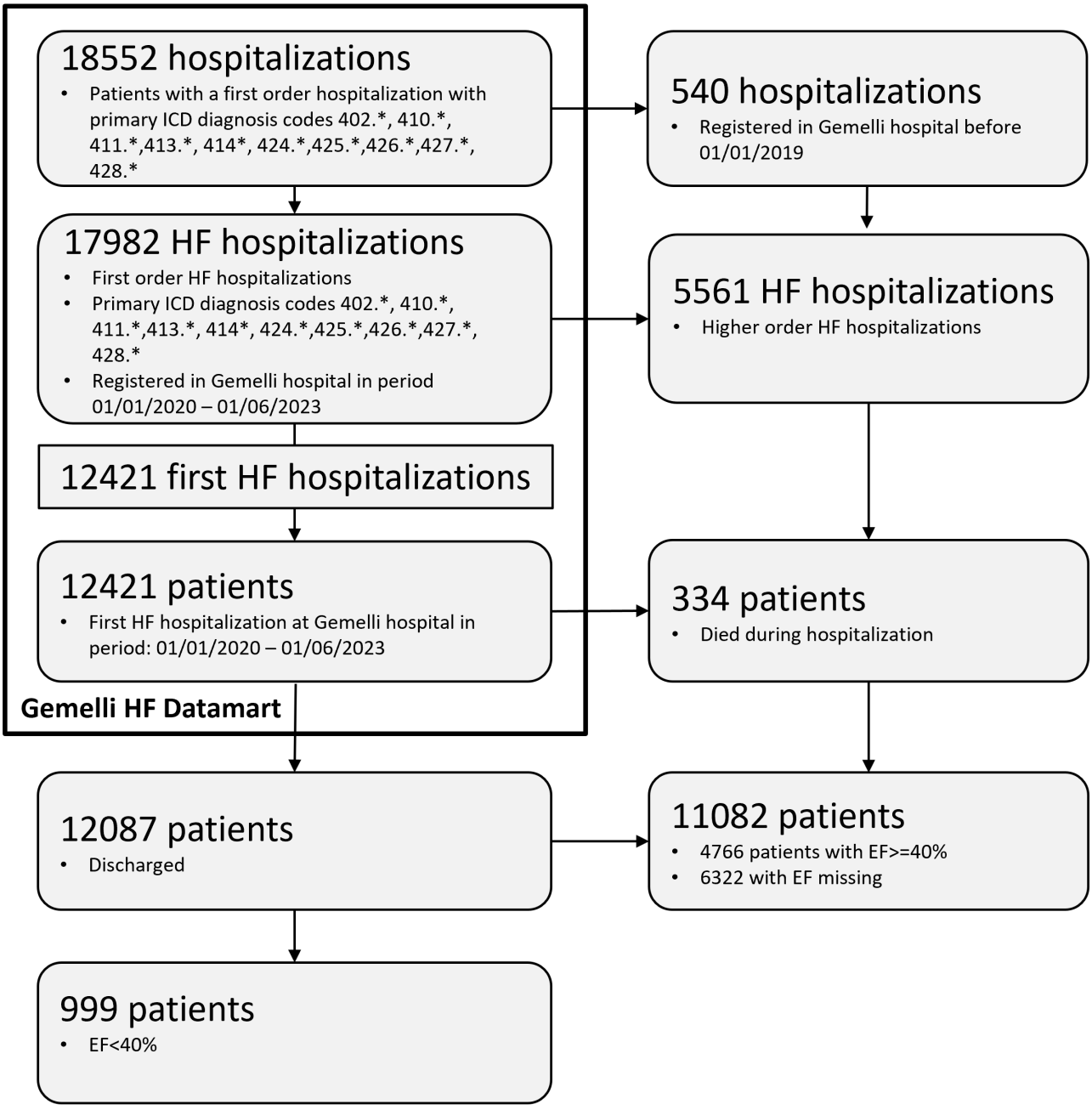

Figure 1 Flow chart of cohort selection. Of 12 421 patients with a first hospitalisation for HF, 999 patients had at least one echocardiographic study documenting an EF of less than 40%. EF, ejection fraction; HF, heart failure; ICD, International Classification of Diseases.

to 1.21)) resulted as independent positive predictors at multivariate analysis (figure 4). In the sensitivity analysis including only ARNi, 'discharge before September 2021' (adjusted OR 0.40; 95% CI (0.30 to 0.54)) was associated with less prescription of it (online supplemental table S7).

Mineralocorticoid receptor antagonist

The independent negative predictors were 'significant renal dysfunction' (adjusted OR 0.44, 95% CI (0.23 to 0.83)) and 'diabetes' (adjusted OR 0.73 95% CI (0.56 to 0.96)), while the only independent positive predictor was the concomitant prescription of 'furosemide' (adjusted OR 1.41, 95% CI (1.04 to 1.91)) (figure 4).

Sodium-glucose cotransporter 2 inhibitor

Independent negative predictors were 'discharge before January 2022' (adjusted OR 0.10, 95% CI (0.06 to 0.17)), 'significant renal dysfunction' (adjusted OR 0.34, 95% CI (0.11 to 0.99)), increasing 'age' (adjusted OR 0.99, 95% CI (0.96 to 0.99)), while independent positive predictors were higher levels of 'haemoglobin' (adjusted OR 1.19, 95% CI (1.10 to 1.29)) and 'diabetes' (adjusted OR 2.31,

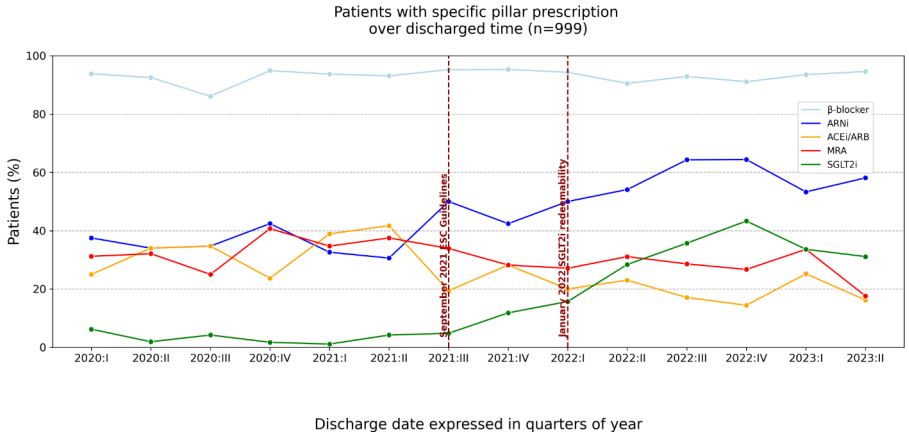

Figure 2 Temporal trends of proportions of patients per drug type. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin–neprilysin receptor inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

95% CI (1.58 to 3.39)) (figure 4). None of the patients with a previous 'genitourinary tract infection' received an SGLT2i at discharge (online supplemental table S5). In the sensitivity analysis in which 'June 2022' was considered as a time point, the upward trend in SGLT2i prescription continued to increase even after it (online supplemental table S6). Considering baseline characteristics, patients receiving SGLT2i are overall less severe, as evidenced by lower levels of NT-proBNP, age and BMI value, but higher haemoglobin and eGFR levels (online supplemental table S8).

Risk of the composite of all-cause death and urgent rehospitalisation within 30 days

The composite of all-cause death and urgent rehospitalisation for all causes within 30 days occurred in 9.2% of the entire cohort, remaining largely constant throughout the study period, with no statistically significant differences across the three study time intervals (online supplemental table S 10A). Urgent readmissions accounted for 73% of the composite endpoint, of which about half (ie, 47.8%) were for worsening HF. Considering 'June 2022' as the third time point, the composite of 30-day all-cause death and readmission rate remained largely unaltered, with no statistically significant differences (online supplemental table S6). At multivariate analysis, prescription at discharge of ACEi/ARB/ARNi (adjusted OR 0.38; 95% CI 0.24 to 0.59; p<0.01) was associated with a lower risk of 30-day all-cause death and urgent readmissions, whereas prescription at discharge of furosemide (adjusted OR 2.25; 95% CI 1.29 to 3.94; p<0.01) or a prior genitourinary tract infection (adjusted OR 4.02; 95% CI 1.67 to 9.68; p<0.01) were associated with an increase in such events (online supplemental table S10B). The above results were consistent even when only urgent 30-day readmissions were included in the clinical endpoint. Prescription of SGLT2i was associated with a trend towards a reduction in 30-day all-cause death and urgent readmissions (5.6% vs 10%, p=0.092) (online supplemental table S9).

DISCUSSION

The main findings of the current work were summarised as follows: (1) after a decompensation event, 16.6%, 5.7%, 61.6% and 63.8% of patients of the overall cohort were eligible but did not receive ACEi/ARB/ARNi, β-blocker, MRA or SGLT2 inhibitor, respectively; (2) over

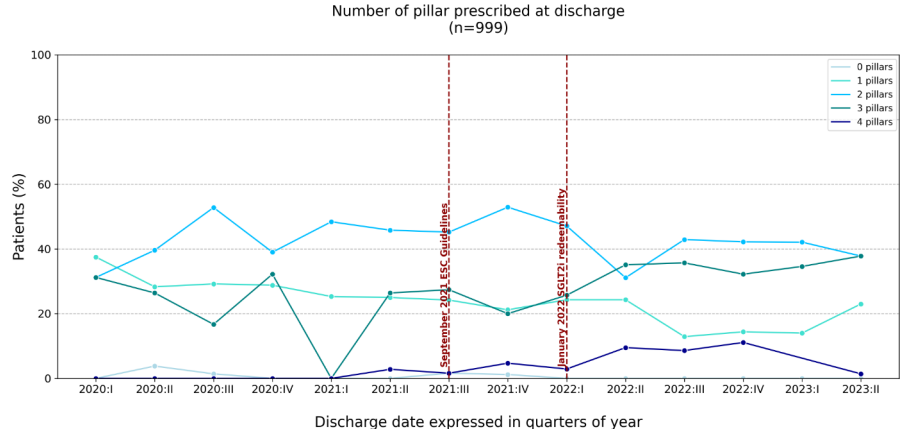

Figure 3 Temporal trends of proportions of patients per number of foundational treatments prescribed.

Table 1 Patterns of prescription according to drug type and presence/absence of cautions and contraindications

Pillar	Prescribed				
	Total patients (n=999)	Before September 2021 (n=416, 41.6%)	Between September 2021 and January 2022 (n=97, 9.7%)	After January 2022 (n=486, 35.0%)	P value
ACEi/ARB/ARNi	731 (73.2%)	288 (69.2%)	70 (72.2%)	373 (76.7%)	**0.039**
ARNi	472 (47.24%)	149 (35.82%)	45 (46.39%)	278 (57.20%)	**0.000**
ACEi/ARB	259 (25.93%)	139 (33.41%)	25 (25.77%)	95 (19.55%)	**0.000**
β-Blocker	928 (92.9%)	385 (92.5%)	93 (95.9%)	450 (92.6%)	0.485
MRA	304 (30.4%)	139 (33.4%)	30 (30.9%)	135 (27.8%)	0.185
SGLT2i	178 (17.8%)	13 (3.1%)	10 (10.3%)	155 (31.9%)	**0.000**
	Possible to prescribe				
ACEi/ARB/ARNi	807 (80.8%)	334 (80.3%)	73 (75.3%)	400 (82.3%)	0.260
β-Blocker	843 (84.4%)	331 (79.6%)	81 (83.5%)	431 (88.7%)	**0.001**
MRA	900 (90.1%)	373 (89.7%)	84 (86.6%)	443 (91.2%)	0.363
SGLT2i	785 (78.6%)	341 (82.0%)	64 (66.0%)	380 (78.2%)	**0.002**
	Possible but not prescribed				
ACEi/ARB/ARNi	166 (16.6%)	80 (19.2%)	14 (14.4%)	72 (14.8%)	0.172
β-Blocker	57 (5.7%)	25 (6.0%)	2 (2.1%)	30 (6.2%)	0.264
MRA	615 (61.6%)	242 (58.2%)	58 (59.8%)	315 (64.8%)	0.115
SGLT2i	637 (63.8%)	329 (79.1%)	54 (55.7%)	254 (52.3%)	**0.000**

Bold values denote statistical significance at the $p < 0.05$ level.
ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2.

time, an increase in prescription was seen only for SGL2i; (3) the composite of 30-day all-cause death and urgent readmission rate was 9.2% and remained stable over time and (4) prescribing an ACEi/ARB/ARNi at discharge was independently associated with a reduction in early urgent readmissions, whereas a previous genitourinary infection

Table 2 Patterns of prescription according to combinations used and drug type

Pillars	Patients (n=999)	Before September 2021 (n=416, 41.6%)	Between September 2021 and January 2022 (n=97, 9.7%)	After January 2022 (n=486, 35.0%)
ACEi/ARB/ARNi+β-blocker	348 (34.8%)	158 (38.0%)	42 (43.3%)	148 (30.5%)
β-Blocker	180 (18.0%)	92 (22.1%)	18 (18.6%)	70 (14.4%)
ACEi/ARB/ARNi+MRA +β-blocker	177 (17.7%)	96 (23.1%)	19 (19.6%)	62 (12.8%)
ACEi/ARB/ARNi +β-blocker+SGLT2i	108 (10.8%)	9 (2.2%)	3 (3.1%)	96 (19.8%)
β-Blocker+MRA	53 (5.3%)	26 (6.2%)	4 (4.1%)	23 (4.7%)
ACEi/ARB/ARNi+MRA+ β-blocker+SGLT2i	43 (4.3%)	4 (1.0%)	4 (4.1%)	35 (7.2%)
ACEi/ARB/ARNi	32 (3.2%)	15 (3.6%)	1 (1.0%)	16 (3.3%)
ACEi/ARB/ARNi+MRA	17 (1.7%)	6 (1.4%)	1 (1.0%)	10 (2.1%)
β-Blocker+SGLT2i	17 (1.7%)	0 (0.0%)	2 (2.1%)	15 (3.1%)
MRA	9 (0.9%)	7 (1.7%)	1 (1.0%)	1 (0.2%)
No pillar	5 (0.5%)	3 (0.7%)	1 (1.0%)	1 (0.2%)
ACEi/ARB/ARNi+MRA+SGLT2i	3 (0.3%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
ACEi/ARB/ARNi+SGLT2i	3 (0.3%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
β-Blocker+MRA+SGLT2i	2 (0.2%)	0 (0.0%)	1 (1.0%)	1 (0.2%)
SGLT2i	2 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.4%)

ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter 2.

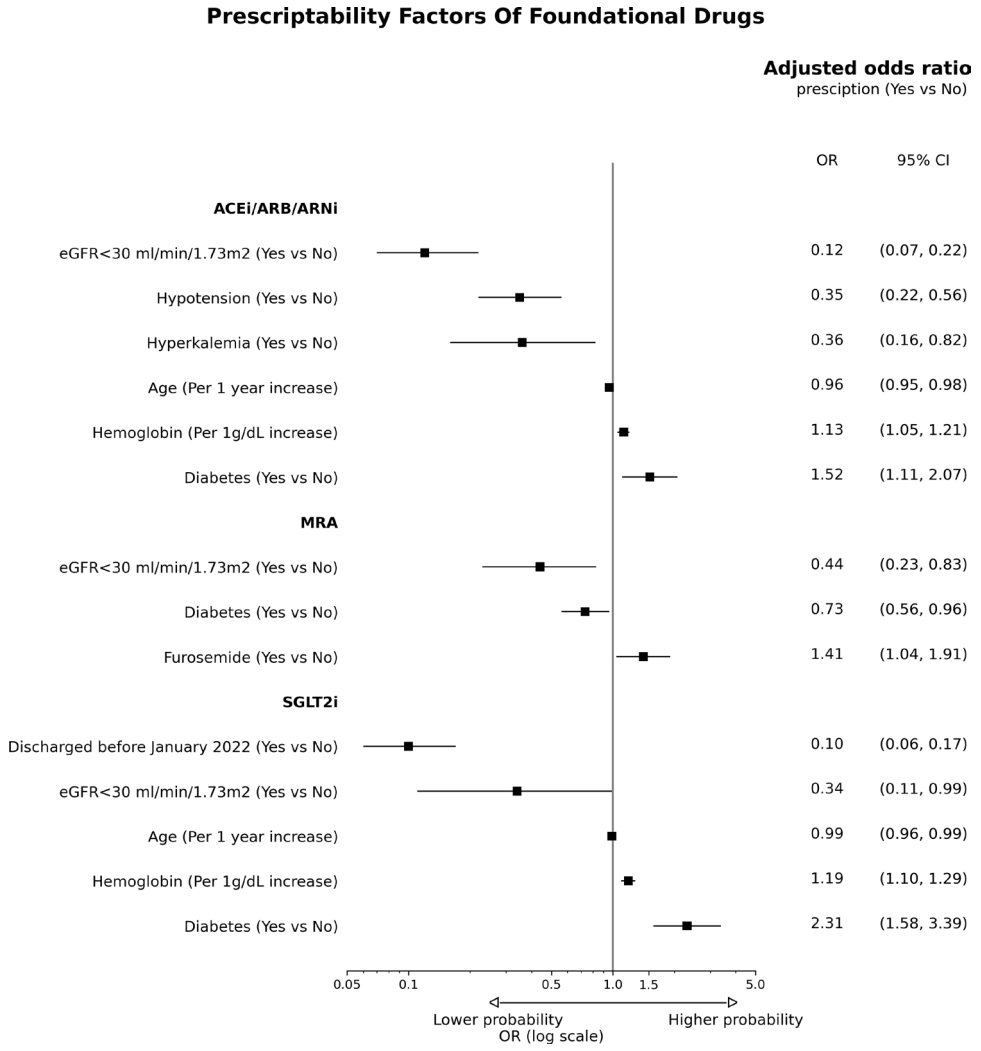

Figure 4 Prescriptability factors of foundational drugs. ACEi, ACE inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin-neprilysin receptor inhibitor; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

or furosemide prescription at discharge were associated with an increase of this outcome.

Actual prescription, eligibility and predictors of prescription

Some registries analysed the prescription of GRMT at discharge in patients hospitalised for HFrEF. Most of these were conducted before the release of the ESC HF 2021 guidelines, examined the prescription for only one of the four foundational therapies or do not focus on the subtype with reduced EF.[8–16]

Beta-blockers

Compared with other large registries enrolling patients hospitalised for HFrEF, the prescription rate in our cohort was among the highest (online supplemental table 11). Overall, our analysis confirms how the intrahospital use of beta-blockers is both feasible, given the low number of cautions/contraindications in a real-world population, and well established in daily clinical practice, as shown by the high number of prescriptions, resulting in the highest among the drugs analysed.

ACEi/ARB/ARNI

In our cohort, the prescription rate is one of the highest in comparison to other registries (online supplemental table S11). In accordance with data from three other large observational registries, hyperkalaemia, hypotension, significant renal dysfunction (ie, eGFR<30 mL/min), and older age resulted to be associated with less prescription of ACEi/ARB/ARNI.[11 17 18] However, in real-world practice, concern may exceed the actual risk. Fear of hypotension, worsening renal failure or hyperkaliaemia, especially in elderly patients, emerged as one of the major limiting factors in the implementation of GRMT, putting patients at greater risk for adverse outcomes.[3] Although several years have passed since the approval of ACEi/ARB/ARNi and reassuring data on their efficacy and safety also in the elderly, further efforts are needed to address their underuse. Consistently with other studies, diabetes was found to be a driving factor associated with ACE/ARB/ARNi prescription, probably due to its effect on the progression of diabetic nephropathy.[19] In addition, ARNis

exhibited a direct effect on glycaemic control, which may further explain their wider use in diabetic patients.[20]

Mineralocorticoid receptor antagonist

Compared with other large contemporary registries, our cohort exhibited the lowest rate of prescription[8–11 13] (online supplemental table S11). This finding shows the persistent inertia in prescribing MRA, which probably stems from both concern about inducing hyperkalaemia or worsening renal function and a lack of education and promotion of its indication.[21] At multivariate analysis, the presence of 'significant renal dysfunction' and 'diabetes' was associated with less prescription, while concomitant furosemide use was positively associated with the prescription of MRA at discharge. Although the beneficial effects of MRA were consistent in patients with diabetes with HFrEF, its limited use in patients with diabetes probably reflects the concern of inducing hyperkalaemia, especially in patients with concomitant chronic renal disease. Conversely, a positive association between the prescription of furosemide and MRA was also reported in the Swedish HF registry.[22] One possible explanation of this finding could be that MRA may have been used to compensate for potassium excretion due to loop diuretics, especially in patients with more severe HF.

Sodium-glucose cotransporter 2 inhibitor

Compared with other contemporary registries, our cohort had the lowest prescription rate, despite a considerable increase over time (online supplemental table 11).[8 23] It may be due to the diffuse optimism generated by the growing evidence of their efficacy and safety in acutely decompensated HF patients, as well as by the rapid approval process for reimbursability by the competent authorities in our country.[12 24] Of note, among the positive predictors of SGLT2i prescription, there was 'discharge after January 2022', when the drug became reimbursable in Italy for HFrEF patients. This finding demonstrates how the lack of reimbursement constitutes a barrier to the use of novel drugs, despite guideline recommendations, representing therefore a key step that should follow guideline approval as soon as possible. As in the Swedish HF Registry and the GWTG HF Registry, diabetes, age and haemoglobin levels were predictors of SGLT2i prescription.[8 23] The positive association with diabetes probably reflects the fact that patients with HFrEF and diabetes have a dual indication for this treatment, which may facilitate a more rapid adoption. Furthermore, lower levels of haemoglobin or older age may reflect a higher number of comorbidities or multiorgan impairment, which may be associated with lower adherence to new medications.[25] Finally, a history of 'genitourinary tract infection' emerged as a key barrier to real-world implementation of SGLT2i, as none of the patients in our cohort with a history of infection received it. This finding was echoed in another study, in which urogenital infection was reported as the most common adverse event of concern to physicians,[26] although recent meta-analyses and large registries have downgraded the risk of this adverse event.[4 27]

30-day all-cause death and urgent readmission

In our cohort, the rate of the composite of 30-day all-cause death and urgent readmissions was 9.2% and remained stable over the study period, despite an increase in SGLT2i prescription. However, its prescription has been increasingly shifted towards patients with a less severe form of HFrEF, which per se carries a lower risk of adverse cardiovascular events. This finding is consistent with other studies, showing a lack of reduction in early rehospitalisations and all-cause death over the years, although the available therapeutic armamentarium has been expanded.[28–30] In our analysis, the prescription of ACE/ARB/ARNi at discharge was associated with a reduction in 30-day all-cause death and urgent readmissions, whereas the prescription of loop diuretics at discharge or a previous genitourinary infection was associated with an increase in them. The benefit of ACE/ARBs/ARNis is expected and is consistent with data from the PARADIGM-HF trial and real-world studies showing a reduction in early readmissions with ARNi and ACE/ARBs, respectively.[31 32] Conversely, although loop diuretics have been widely indicated to reduce signs and symptoms of congestion in patients with HFrEF, their prognostic impact is more controversial, with no RCT demonstrating a clear benefit on clinical outcomes.[2] Similar to our study, other ones have shown an increased risk of adverse cardiovascular events in patients receiving diuretics at discharge.[33–38] Specifically, our study has the value of shedding light on early adverse events (ie, within 30 days after discharge). One possible explanation is that the excessive use of diuretics may hamper the implementation of GRMT, probably due to the promotion of hypovolaemia, hypotension or worsening renal function, as shown in the BIOSTAT-HF study.[33] Second, diuretics prescription may alter the hydroelectrolyte imbalance, leading to the occurrence of hypotension/hypovolaemia, dyselectrolycaemia and neurohormonal activation, which, ultimately, results in an increased risk of adverse events.[39 40] Third, some of the patients receiving furosemide at discharge may have developed resistance to diuretics, dampening their overall effectiveness.[41] However, given the observational nature of the study, selection bias cannot be excluded, as patients with an advanced form of HFrEF and therefore a higher risk of rehospitalisation are more likely to receive diuretics. Nevertheless, it was, at least partially, mitigated, through an extensive multivariable adjustment for key baseline variables, including nt-proBNP and haemoglobin, which are also related to congestion. The association between a prior genitourinary infection and the risk of early urgent readmission may have several explanations. First, it could be explained by the non-prescription of SGLT2i. Indeed, in our cohort, none of the patients with a history of genitourinary infection received this drug at discharge. Second, a previous infection could per se worsen the prognosis of HF patients.[42] Of note, our

study is the first to show how their negative impact occurs within the first 30 days after hospitalisation, highlighting a subset of patients at higher risk of early readmission. Among the four foundational therapies, only ACE/ARB/ARNi showed a positive prognostic effect. The lack of beneficial effects of beta-blockers may be easily explained because they are prescribed to the vast majority of our cohort. For MRAs and SGLT2i, however, there are several possible explanations. Regarding MRA, its beneficial effect may be blunted by the common coadministration with furosemide, which instead was associated with a worsened prognosis. Regarding SGLT2i, it tends to be prescribed to patients with a less severe form of HF, where their beneficial effects may be dampened due to *a* priori lower risk of adverse outcomes. In addition, our study may be underpowered to detect a benefit of SGLT2 inhibitor for this outcome, given the small percentage of patients (ie, 17.8%) receiving it at discharge.

Limitations

Our study has several limitations. First, we report the experience of a single tertiary referral centre, but there may be some variability in treatment approaches among care providers, despite the existence of globally shared guidelines. In addition, as a tertiary centre, it may attract more severe patients whose characteristics may deviate from the average, introducing a selection bias. Second, we were unable to assess the admission to other centres within 30 days of discharge. Third, we evaluated only therapy at discharge, without considering changes in therapy from admission and without considering dosing, although both therapeutic trajectories and dosing may influence the eligibility and prognostic impact of the four foundational therapies. Fourth, given the observational and retrospective design of the study, the influence of unknown factors cannot be excluded despite adjustment for known confounders. Fifth, as the outcome was represented by all-cause urgent readmissions, we cannot exclude potential unmeasured confounders related to hospitalisations of non-cardiac causes. Sixth, diagnosis is based on ICD-9 codes, which do not have 100% specificity and sensitivity for detecting HF, and the exclusive inclusion of patients with a documented EF value may have further reduced diagnostic sensitivity.

CONCLUSIONS

In patients admitted with a primary diagnosis of HFrEF, early adoption of GRMT is still constrained, with a significant increase in SGLT2i prescriptions after January 2022 and a lower risk of the composite of all-cause death and urgent early readmissions restricted to the use of ACEi/ARB/ARNi.

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