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RESEARCH ARTICLE

Guideline-directed medical therapy in severe heart failure with reduced ejection fraction: an analysis from the HELP-HF registry

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Aim Persistent symptoms despite guideline-directed medical therapy (GDMT) and poor tolerance of GDMT are hallmarks of patients with advanced heart failure (HF) with reduced ejection fraction (HFrEF). However, real-world data on GDMT use, dose, and prognostic implications are lacking.

Methods and results We included 699 consecutive patients with HFrEF and at least one 'I NEED HELP' marker for advanced HF enrolled in a multicentre registry. Beta-blockers (BB) were administered to 574 (82%) patients, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor–neprilysin inhibitors (ACEi/ARB/ARNI) were administered to 381 (55%) patients and 416 (60%) received mineralocorticoid receptor antagonists (MRA). Overall, ≥50% of target doses were reached in 41%, 22%, and 56% of the patients on BB, ACEi/ARB/ARNI and MRA, respectively. Hypotension, bradycardia, kidney dysfunction and hyperkalaemia were the main causes of underprescription and/or underdosing, but up to a half of the patients did not receive target doses for unknown causes (51%, 41%, and 55% for BB, ACEi/ARB/ARNI and MRA, respectively). The proportions of patients receiving BB and ACEi/ARB/ARNI were lower among those fulfilling the 2018 HFA-ESC criteria for advanced HF. Treatment with BB and ACEi/ARB/ARNI were associated with a lower risk of death or HF hospitalizations (adjusted hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.48–0.84, and HR 0.74, 95% CI 0.58–0.95, respectively).

Conclusions In a large, real-world, contemporary cohort of patients with severe HFrEF, with at least one marker for advanced HF, prescription and uptitration of GDMT remained limited. A significant proportion of patients were undertreated due to unknown reasons suggesting a potential role of clinical inertia either by the prescribing healthcare professional or by the patient. Treatment with BB and ACEi/ARB/ARNI was associated with lower mortality/morbidity.

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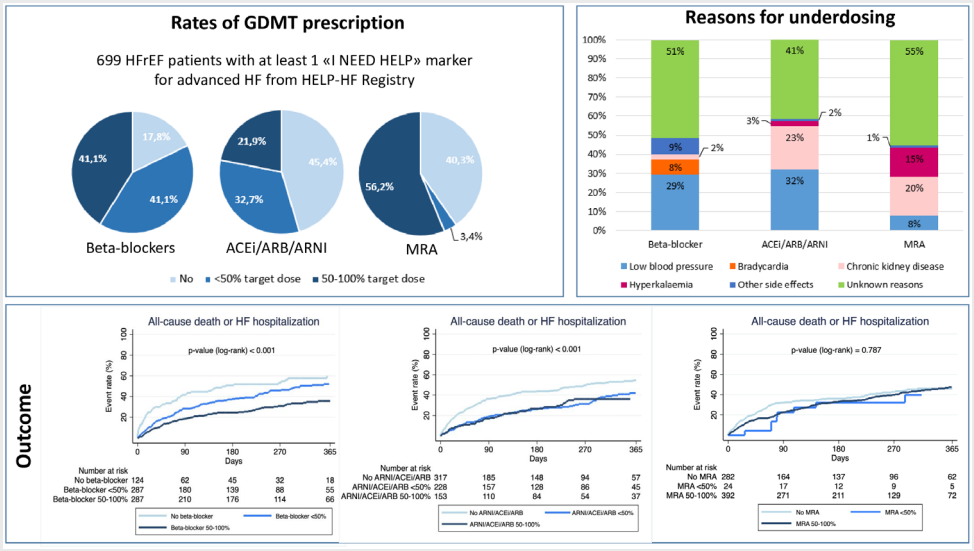
Graphical Abstract



Rates of guideline-directed medical therapy (GDMT) prescription in real-world patients with severe heart failure (HF) with reduced ejection fraction (HFrEF), reasons for underdosing and association with outcome. Upper left panel: rates of GDMT prescription and dosing, including beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitors (ACEi/ARB/ARNI) and mineralocorticoid receptor antagonists (MRA). Upper right panel: reasons for underdosing of beta-blockers, ACEi/ARB/ARNI and MRA. Lower panels: Kaplan–Meier curves for 1-year all-cause death or HF hospitalization according to beta-blockers, ACEi/ARB/ARNI and MRA prescription and dosing.

Keywords Advanced heart failure • Severe heart failure • Heart failure with reduced ejection fraction • Guideline-directed medical therapy • Evidence-based medical therapy • Prescription • Prognosis

Introduction

Guideline-directed medical therapy (GDMT) consisting of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, mineralocorticoid receptor antagonists (MRA) and, more recently, angiotensin receptor–neprilysin inhibitors (ARNI) and sodium–glucose cotransporter 2 (SGLT2) inhibitors, has consistently improved the prognosis of patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1,2] However, many patients continue to progress to a late stage of advanced HF, characterized by severe symptoms, poor quality of life and high hospitalizations and mortality rates.[3–5] Although GDMT is indicated also in these patients, it is often poorly tolerated and therefore its use in patients with advanced HF may be limited.[6–14]

The aim of the current study was to assess the use, dosing and causes of suboptimal use of GDMT in a real-world, contemporary, population of patients with severe HFrEF enrolled in the Assessment of the I Need Help markers in Heart failure (HELP-HF) registry, and to evaluate the associations of treatment use with mortality/morbidity.

Methods

Study design and data collection

The design of the HELP-HF registry has been previously described.[15] Briefly, HELP-HF was an observational, retrospective, multicentre registry including all consecutive patients who were hospitalized for acute HF or were evaluated as outpatients for chronic HF at four Italian high-volume centres between 1 January 2020 and 30 November 2021, and had at least one of the 'I NEED HELP' high-risk markers for advanced HF.[15] Institutional review board approval was waived for this registry because of its retrospective design with collection of anonymized data and no use of any study-specific intervention. De-identified individual patient data on medical history, clinical presentation, echocardiography and laboratory findings, medical therapy and clinical outcomes were collected.

Assessment of guideline-directed medical therapy

Baseline use and dose of the following HFrEF medication classes were examined: (1) beta-blockers; (2) ACEi, ARB or ARNI; and (3) MRA. For the purpose of our study, SGLT2 inhibitors were not evaluated

as data collection occurred mostly before their indication for HFrEF treatment and introduction in guidelines.

For each medication class, the reasons of non-prescription or underdosing were determined based on the documentation in the medical records or as ascertained by study investigators. For each patient and each medication, available dose information was reviewed, and patients who received medications, were divided into two groups according to dose: <50% or ≥50% of target dose. The fractional dose (%) of the target dose was reported. Target dose was defined as in the current European Society of Cardiology (ESC) HF guidelines (online supplementary *Table S1*).[1] In an additional analysis, we assessed GDMT prescription in the subset of patients fulfilling the 2018 Heart Failure Association (HFA)-ESC criteria for advanced HF.

Study endpoints

The primary endpoint of the study was a composite of all-cause mortality or HF hospitalization. We also investigated all-cause mortality as a separate outcome.

Statistical analyses

Continuous variables were reported as means ± standard deviation or median and interquartile range (IQR), according to their distribution. Categorical variables were recorded as frequencies and percentages.

To assess the independent associations between patient characteristics and the likelihood of medical therapy use and dose, multivariable logistic regression analyses were performed, with no use of each drug and use of underdosed drug (<50% of the target dose) as dependent variables, separately. Patient characteristics which were associated with the dependent variable at the univariable models with a p-value <0.10 or considered relevant according to clinical judgment were included in multivariable logistic regression models. Odds ratio (OR) and 95% confidence interval (CI) were calculated.

The first occurrence of the primary composite endpoint and of all-cause mortality was evaluated in patients not prescribed versus prescribed with each medication and reaching versus not reaching ≥50% of the target dose using the Kaplan–Meier method and the log-rank test. Multivariable Cox proportional hazards models were performed to assess the association between GDMT prescription/dosing and the outcomes and included the variables previously included in a prognostic model derived in the HELP-HF study: age, sex, HFA-ESC definition of advanced HF, inpatient versus outpatient status, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease (COPD), New York Heart Association (NYHA) functional class III or IV, systolic blood pressure, estimated glomerular filtration rate and heart rate (the latter one was included in the model for mortality only).[15] Results of the Cox regression analyses were reported as hazard ratio (HR) and 95% CI.

All reported p-values were 2-sided, and a $p < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA version 13.0 (Stata Corp., College Station, TX, USA).

Results

Study population

Out of 1149 patients with HF that presented at least one high-risk 'I NEED HELP' marker, 699 (61%) had a left ventricular ejection fraction (LVEF) ≤40% (HFrEF) and were included in the present analysis. Baseline characteristics of the study population are reported in *Table 1*. The mean age was 73.2 ± 11.7 years and 76% of patients were male. At the time of enrolment, 498 patients (71.2%) were hospitalized, and 106 (15.2%) patients had new-onset (*de novo*) HF. Most patients ($n = 450$, 64%) were in NYHA class III–IV. Mean LVEF was 27.3 ± 7.6% and median (IQR) N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 6750 (3490–15 072) pg/ml (*Table 1*).

Guideline-directed medical therapy prescription

Overall, 574 (82.2%), 381 (54.6%), and 416 (59.6%) patients were treated with beta-blockers, ACEi/ARB/ARNI, and MRAs, respectively (*Table 2*). A total of 184 (26.4%) patients were on ARNI. Two and three GDMT agents were administered to 485 (69.5%) and 241 (34.5%) of the patients, respectively. Specifically, 48.4% of patients received beta-blockers and ACEi/ARB/ARNI, 52.7% beta-blockers and MRA, and 37.4% ACEi/ARB/ARNI and MRA. The proportion of patients who received ≥50% target dose of beta-blocker and ACEi/ARB/ARNI was 41.1% and 21.9%, respectively, whereas the majority of patients (56.2%) received ≥50% target dose of MRA (*Table 2*).

Reasons for no prescription of treatments or sub-optimal GDMT prescription (i.e. <50% target dose) are reported in *Table 2*. About 30% of patients did not receive beta-blockers due to low systolic blood pressure and 8.9% due to bradycardia. Chronic kidney disease (CKD) (36%) was the most frequent reason for ACEi/ARB/ARNI non-prescription followed by hypotension (23%). CKD and history of hyperkalaemia were the most frequent reasons for underprescription of MRA (20.9% and 14.5%, respectively). Similar reasons were reported for underdosing (*Table 2*). Of note, reasons for beta-blockers, ACEi/ARB/ARNI and MRA non-prescription were unknown in 45.9%, 36.9%, and 56.0% of patients, respectively. Similarly, reasons for underdosing were unknown in a large proportion of patients for beta-blockers, ACEi/ARB/ARNI and MRA (51.2%, 41.4%, and 55.3%, respectively) (*Graphical Abstract*, *Table 2*).

Patients fulfilling the 2018 HFA-ESC criteria for advanced heart failure

Among patients fulfilling the 2018 HFA-ESC definition for advanced HF, 76.8%, 50.3%, and 66.9% were treated with beta-blockers, ACEi/ARB/ARNI and MRAs, and 33.1%, 22.5%, and 64.9% received ≥50% of the target dose, respectively (online supplementary *Table S2*). Forty-two patients (27.8%) were on ARNI. Two and three GDMT agents were administered to 67.6% and 32.4% of patients, respectively. Hypotension was the most common reason for beta-blockers and ACEi/ARB/ARNI non-prescription (40% and 32%, respectively) or underdosing (41.6% and 43.6%). ACEi/ARB/ARNI and MRA were not prescribed due to CKD in 29.3% and 24% of patients, respectively. Reasons for underprescription and underdosing were, however, unknown in a large proportion of cases (online supplementary *Table S2*).

Table 1 Patient baseline characteristics

No. of patients	699
Inpatients	498 (71.2)
Demographics	
Male sex	529 (75.7)
Age (years)	73.2 ± 11.7
BMI (kg/m^2)	28.4 ± 22.7
Medical history	
Hypertension	467 (66.8)
Dyslipidaemia	382 (54.7)
Diabetes mellitus	273 (39.1)
Peripheral artery disease	126 (18.0)
Prior stroke/TIA	101 (14.5)
Prior atrial fibrillation	355 (50.8)
COPD	147 (21.0)
CKD	396 (56.8)
History of cancer	148 (21.2)
Cognitive impairment	71 (10.2)
Ischaemic heart disease	380 (54.4)
Prior valve surgery	69 (9.9)
Prior percutaneous valve intervention	55 (7.9)
Known cardiomyopathy	175 (25.0)
Prior device implantation	385 (55.1)
PM	59 (8.4)
ICD	166 (23.8)
CRT-P	9 (1.3)
CRT-D	151 (21.6)
Clinical assessment	
NYHA functional class III–IV	450 (64.4)
Systolic blood pressure (mmHg)	120 ± 26
Diastolic blood pressure (mmHg)	72 ± 15
Mean blood pressure (mmHg)	88 ± 18
Heart rate (bpm)	81 ± 22
Loop diuretics	608 (87.1)
De novo HF diagnosis	106 (15.2)
At least one HF hospitalization within last year	264 (37.8)
Months since HF diagnosis	48 (5–111)
Fulfilling all 4 updated 2018 HFA-ESC criteria for advanced HF	152 (21.8)
INTERMACS profiles 1–3	85 (12.2)
ACC/AHA stage D	143 (20.5)
Laboratory findings	
Haemoglobin (g/dl)	12.5 ± 2.2
Haematocrit (%)	38.2 ± 6.6
Creatinine (mg/dl)	1.5 (1.1–2.1)
eGFR CKD-EPI (ml/min/1.73 m^2)	42 (27–61)
eGFR CKD-EPI <30 ml/min/1.73 m^2	199 (29.3)
Blood urea nitrogen (mg/dl)	69 (46–109)
NT-proBNP (pg/ml)	6750 (3490–15 072)
Na (mmol/L)	140 (137–142)
K (mmol/L)	4.1 (3.8–4.6)
Cl (mmol/L)	101 (98–104)
Echocardiographic data	
LVEF (%)	27.3 ± 7.6
Moderate to severe MR	464 (68.2)
RV dilatation	209 (33.0)
RV dysfunction	338 (50.1)

Data are presented as *n* (%), mean ± standard deviation, or median (Q25–Q75). ACC, American College of Cardiology; AHA, American Heart Association; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; eGFR, estimated glomerular filtration rate; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HF, heart failure; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; RV, right ventricular; TIA, transient ischaemic attack.

Table 2 Use of guideline-directed medical therapy

	Beta-blockers	ACEi/ARB/ARNI	MRA
Treated patients	574 (82.2)	381 (54.6)	416 (59.6)
Dose ≥50% of the target dose	287 (41.1)	153 (21.9)	392 (56.2)
Fractional dose, %	49.5 ± 33.6	46.5 ± 38.1	85.6 ± 62.2
Reasons for lack of treatment			
Low blood pressure	38 (30.7)	73 (23.0)	21 (7.5)
Bradycardia	11 (8.9)	–	–
Chronic kidney disease	6 (4.8)	114 (36.0)	59 (20.9)
Hyperkalaemia	–	6 (1.9)	41 (14.5)
Other side effects	11 (8.9)	7 (2.3)	3 (1.1)
Unknown reasons	57 (45.9)	117 (36.9)	158 (56.0)
Reason for underdosing (<50% target dose)			
Low blood pressure	120 (29.2)	174 (31.9)	24 (7.8)
Bradycardia	34 (8.3)	–	–
Chronic kidney disease	10 (2.4)	123 (22.6)	62 (20.3)
Hyperkalaemia	–	14 (2.6)	47 (15.4)
Other side effects	35 (8.6)	8 (1.5)	3 (1.0)
Unknown reasons	211 (51.2)	226 (41.4)	170 (55.3)

Data are presented as *n* (%), mean ± standard deviation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

Predictors of lack of treatment

Independent predictors of lack of prescription of GDMT are shown in *Tables 3–5*. NYHA functional class III or IV (OR 2.17; 95% CI 1.11–4.24) and cardiogenic shock at presentation (OR 2.02; 95% CI 1.08–3.81) were associated with a higher probability of beta-blockers non-prescription, whereas an ischaemic aetiology of HF was associated with a lower probability of being not prescribed with beta-blockers (OR 0.54; 95% CI 0.30–0.98). Severe kidney dysfunction, defined as an estimated glomerular

Table 3 Predictors of beta-blocker non-prescription and underdosing

	Predictors of beta-blocker non-prescription				Predictors of beta-blockers underdosing (<50% of target dose)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years)	1.01 (0.99–1.02)	0.417	1.02 (0.997–1.05)	0.082	1.01 (1.00–1.02)	0.101	1.01 (0.99–1.04)	0.177
Female sex	1.22 (0.78–1.89)	0.381	1.18 (0.61–2.27)	0.627	1.03 (0.72–1.46)	0.872	0.96 (0.55–1.70)	0.901
BMI (kg/m^2)	1.00 (1.00–1.01)	0.336			1.00 (0.99–1.00)	0.401		
Type of inclusion (inpatients)	3.48 (1.98–6.14)	**<0.001**	0.89 (0.34–2.31)	0.809	2.76 (1.97–3.86)	**<0.001**	2.01 (1.08–3.75)	**0.027**
Ischaemic HF aetiology	0.48 (0.33–0.72)	**<0.001**	0.54 (0.30–0.98)	**0.041**	0.77 (0.56–1.04)	0.085	0.91 (0.57–1.46)	0.702
COPD	0.94 (0.58–1.52)	0.787			1.52 (1.04–2.23)	**0.032**	2.01 (1.06–3.81)	**0.032**
De novo HF	2.95 (1.86–4.67)	**<0.001**	1.27 (0.54–3.01)	0.587	1.36 (0.89–2.10)	0.159		
NYHA class III or IV	1.75 (1.13–2.70)	**0.012**	2.17 (1.11–4.24)	**0.024**	1.57 (1.15–2.15)	**0.005**	1.34 (0.82–2.19)	0.241
Cardiogenic shock	2.86 (1.83–4.45)	**<0.001**	2.02 (1.08–3.81)	**0.028**	2.74 (1.74–4.31)	**<0.001**	1.61 (0.89–2.92)	0.117
HR (bpm)	1.02 (1.01–1.03)	**<0.001**	1.02 (1.01–1.03)	**0.004**	1.02 (1.01–1.02)	**<0.001**	1.00 (0.99–1.02)	0.469
SBP (mmHg)	1.00 (0.99–1.01)	0.981			1.00 (1.00–1.01)	0.500		
HFA-ESC advanced HF definition	1.55 (0.999–2.41)	**0.050**	1.79 (0.96–3.34)	0.065	1.54 (1.06–2.26)	**0.025**	1.26 (0.76–2.10)	0.372
LVEF (%)	1.00 (0.97–1.02)	0.848	1.02 (0.98–1.06)	0.258	0.98 (0.96–1.00)	0.095	0.99 (0.96–1.02)	0.599
Moderate to severe MR	0.86 (0.57–1.31)	0.496			1.17 (0.84–1.62)	0.348		
RV dysfunction	1.23 (0.82–1.83)	0.311			1.26 (0.93–1.72)	0.138		
eGFR <30 ml/min/1.73 m^2	1.00 (0.65–1.53)	0.982			1.04 (0.74–1.46)	0.823		
log NT-proBNP (pg/ml)	1.24 (0.98–1.58)	0.072	1.09 (0.83–1.43)	0.542	1.29 (1.06–1.57)	**0.012**	1.06 (0.88–1.29)	0.386
Haemoglobin (g/dl)	0.93 (0.85–1.02)	0.150			0.98 (0.91–1.06)	0.624		

Bold values indicate statistical significance.

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HR, heart rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure; RV, right ventricular.

filtration rate <30 ml/min/m^2, was a strong independent predictor of ACEi/ARB/ARNI and MRA non-prescription (3.98; 95% CI 2.23–7.09 and OR 2.98; 95% CI 1.68–5.28, respectively).

Predictors of guideline-directed medical therapy underdosing

Independent predictors of GDMT underdosing (defined as doses <50% of the target doses) are shown in *Tables 3–5*. COPD (OR 2.01; 95% CI 1.06–3.81) and inpatient status at inclusion (OR 2.01; 95% CI 1.08–3.75) were associated with a higher probability of achieving <50% of beta-blocker target doses. Markers of more advanced stages of HF (i.e. NYHA functional class, higher NT-proBNP levels, or cardiogenic shock at presentation) were associated with lower beta-blocker doses at univariable analyses but not after adjustments. Cardiogenic shock at presentation (OR 2.27; 95% CI 1.10–4.68), an estimated glomerular filtration rate <30 ml/min/m^2 (OR 1.81; 95% CI 1.12–2.92) and moderate-to-severe mitral regurgitation (OR 1.80; 95% CI 1.20–1.69) were independent predictors of ACEi/ARB/ARNI use at a dose <50% of the target dose. Severe kidney dysfunction was also independently associated with a higher likelihood of MRA underdosing (OR 3.02, 95% CI 1.73–5.29).

Prognostic impact of guideline-directed medical therapy

After a median follow-up of 244 days (IQR 91–380 days), all-cause death or an HF hospitalization occurred in 301 patients (43.0%), and 173 patients (24.8%) died.

Beta-blocker prescription was associated with a lower unadjusted risk of the composite endpoint of all-cause death or HF hospitalization (HR 0.58; 95% CI 0.44–0.76) as well as of all-cause death alone (HR 0.42; 95% CI 0.30–0.58). Patients receiving ≥50% of the target dose where at lower risk of outcome than those receiving a lower dose (*Table 6* and online supplementary *Table S3*). The unadjusted HRs for ACEi/ARB/ARNI prescription compared to non-prescription were 0.59 (95% CI 0.45–0.74) and 0.45 (95% CI 0.33–0.61) for the composite endpoint and for all-cause death, respectively. Subjects receiving ≥50% or <50% of the target dose of ACEi/ARB/ARNI had a similar reduction in the risk of events (HR 0.56 and 0.61, respectively) than those not prescribed with ACEi/ARB/ARNI (*Table 6* and online supplementary *Table S3*). MRA prescription was not significantly associated with outcome (HR 0.94, 95% CI 0.75–1.18 for the composite endpoint) and had a non-significant association with all-cause death (HR 0.76, 95% CI 0.56–1.02). *Figures 1–3* show Kaplan–Meier curves for the 1-year primary composite endpoint of all-cause mortality or HF hospitalization in patients stratified according to non-prescription, prescription of <50% or of ≥50% of target doses for each medication. The Kaplan–Meier curves for all-cause mortality are reported in online supplementary *Figures S1–S3*.

After multivariable adjustment, treatment with beta-blockers (adjusted HR for the composite endpoint 0.63, 95% CI 0.48–0.84) and treatment with ACEi/ARB/ARNI (adjusted HR for the composite endpoint 0.74, 95% CI 0.58–0.95) were significantly associated with lower risk of outcomes (*Table 6* and online supplementary *Table S3*). Patients receiving ≥50% of beta-blocker target dose reported lower risk of events (adjusted HR 0.54, 95% CI 0.39–0.74

Table 4 Predictors of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor non-prescription and underdosing

	Predictors of ACEi/ARB/ARNI non-prescription				Predictors of ACEi/ARB/ARNI underdosing (<50% of target dose)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years)	1.03 (1.02–1.05)	**<0.001**	1.01 (0.99–1.03)	0.251	1.01 (0.99–1.02)	0.486	1.00 (0.99–1.02)	0.789
Female sex	1.45 (1.02–2.04)	**0.037**	1.39 (0.79–2.44)	0.253	1.35 (0.87–2.09)	0.183	1.39 (0.85–2.27)	0.189
BMI (kg/m^2)	1.00 (0.99–1.01)	0.888			1.00 (0.99–1.01)	0.988		
Type of inclusion (inpatients)	1.69 (1.21–2.37)	**0.002**	1.44 (0.72–2.90)	0.302	1.85 (1.27–2.69)	**0.001**	1.45 (0.92–2.29)	0.112
Ischaemic HF aetiology	1.07 (0.79–1.44)	0.661			1.11 (0.77–1.59)	0.572		
De novo HF	1.63 (1.07–2.46)	**0.022**	1.63 (0.82–3.23)	**0.162**	1.84 (1.03–3.29)	**0.038**	1.90 (1.02–3.54)	**0.042**
NYHA class III or IV	0.82 (0.60–1.12)	0.209			0.75 (0.51–1.11)	0.148		
Cardiogenic shock	1.53 (1.03–2.26)	**0.035**	1.13 (0.63–2.00)	0.687	3.30 (1.73–6.31)	**<0.001**	2.27 (1.10–4.68)	**0.026**
SBP (mmHg)	0.997 (0.99–1.00)	0.347			0.99 (0.99–1.00)	0.063	0.99 (0.98–1.00)	0.067
HFA-ESC advanced HF definition	1.24 (0.87–1.78)	0.236			0.96 (0.62–1.47)	0.841		
LVEF (%)	1.02 (1.00–1.04)	0.066	1.02 (0.99–1.05)	0.285	0.98 (0.96–1.01)	**0.152**	0.99 (0.96–1.02)	0.542
Moderate to severe MR	1.37 (0.99–1.90)	0.061	1.23 (0.70–2.16)	0.467	2.18 (1.50–3.17)	**<0.001**	1.80 (1.20–1.69)	**0.004**
RV dysfunction	1.14 (0.84–1.55)	0.394			0.90 (0.63–1.30)	0.577		
eGFR <30 ml/min/1.73 m^2	4.04 (2.83–5.76)	**<0.001**	3.98 (2.23–7.09)	**<0.001**	1.85 (1.19–2.89)	**0.007**	1.81 (1.12–2.92)	**0.015**
log NT-proBNP (pg/ml)	1.60 (1.31–1.96)	**<0.001**	1.12 (0.86–1.45)	0.413	1.15 (0.91–1.45)	0.256		
Haemoglobin (g/dl)	0.89 (0.82–0.959)	**0.001**	0.91 (0.81–1.029	0.121	0.94 (0.86–1.03)	0.170		
K^+ (mmol/L)	0.92 (0.72–1.179)	0.490			0.88 (0.66–1.17)	0.375		

Bold values indicate statistical significance.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNO, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure; RV, right ventricular.

Table 5 Predictors of mineralocorticoid receptor antagonist non-prescription and underdosing

	Predictors of MRA non-prescription				Predictors of MRA underdosing (dose <50% of target dose)			
	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age (years)	1.02 (1.00–1.03)	**0.022**	1.00 (0.98–1.02)	0.777	1.02 (1.00–1.03)	**0.015**	1.00 (0.98–1.02)	0.944
Female sex	1.19 (0.84–1.68)	0.339	0.92 (0.52–1.64)	0.782	1.23 (0187-1.73)	0.250	1.02 (0.59–1.77)	0.931
BMI (kg/m^2)	1.00 (0.99–1.01)	0.834			1.00 (0.99–1.01)	0.965		
Type of inclusion (inpatients)	1.84 (1.29–2.60)	**0.001**	1.46 (0.72–2.98)	0.299	1.54 (1.10–2.17)	**0.011**	1.39 (0.71–2.74)	0.339
Ischaemic HF aetiology	0.75 (0.55–1.01)	0.061	0.68 (0.42–1.10)	0.118	0.79 (0.58–1.06)	0.120		
De novo HF	2.61 (1.71–3.99)	**<0.001**	1.80 (0.88–3.69)	0.109	2.31 (1.51–3.53)	**<0.001**	1.66 (0.83–3.33)	0.154
NYHA class III or IV	1.04 (0.76–1.43)	0.797			1.08 (0.79–1.48)	0.615		
Cardiogenic shock	1.16 (0.78–1.73)	0.451			1.15 (0.79–1.70)	0.480		
SBP (mmHg)	1.01 (1.01–1.02)	**<0.001**	1.00 (0.99–1.01)	0.860	1.01 (1.01–1.02)	**<0.001**	1.00 (0.99–1.01)	0.795
HFA-ESC advanced HF definition	0.67 (0.46–0.98)	**0.040**	1.10 (0.63–1.93)	0.742	0.63 (0.43–0.91)	**0.015**	0.99 (0.57–1.69)	0.960
LVEF (%)	1.03 (1.01–1.05)	**0.004**	1.00 (0.97–1.04)	0.841	1.04 (1.02–1.06)	**0.001**	1.02 (0.99–1.05)	0.317
Moderate to severe MR	0.68 (0.49–0.94)	**0.021**	0.83 (0.48–1.43)	0.499	0.72 (0.52–0.99)	**0.044**	0.96 (0.56–1.64)	0.891
RV dysfunction	0.64 (0.47–0.87)	**0.005**	0.50 (0.30–0.82)	**0.007**	0.70 (0.52–0.96)	**0.024**	0.64 (0.39–1.03)	0.068
eGFR <30 ml/min/1.73 m^2	1.88 (1.35–2.63)	**<0.001**	2.98 (1.68–5.28)	**<0.001**	1.79 (1.28–2.50)	**0.001**	3.02 (1.73–5.29)	**<0.001**
log NT-proBNP (pg/ml)	1.27 (1.05–1.54)	**0.016**	1.11 (0.85–1.44)	0.448	1.26 (1.04–1.52)	**0.018**	1.07 (0.83–1.38)	0.597
Heamoglobin (g/dl)	0.92 (0.86–0.99)	**0.028**	0.91 (0.81–1.03)	0.141	0.94 (0.88–1.01)	0.108		
Na^+ (mmol/L)	1.05 (1.01–1.09)	**0.017**	1.05 (1.00–1.10)	0.061	1.05 (1.01–1.09)	**0.013**	1.04 (0.99–1.10)	0.096
K^+ (mmol/L)	1.10 (0.87–1.41)	0.423			1.13 (0.89–1.44)	0.320		

Bold values indicate statistical significance.

BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFA-ESC, Heart Failure Association of the European Society of Cardiology; HR, heart rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure; RV, right ventricular.

Table 6 Univariable and multivariable models for the composite of all-cause death or heart failure hospitalization

	Univariate		Multivariate*	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Beta-blocker use (any dose)	0.58 (0.44–0.76)	**<0.001**	0.63 (0.48–0.84)	**0.001**
Beta-blocker dose ≥50% target dose vs. no therapy or <50% target dose	0.58 (0.46–0.74)	**<0.001**	0.68 (0.53–0.88)	**0.003**
Beta-blockers dose categories				
≥50% target dose vs. no therapy	0.46 (0.34–0.63)	**<0.001**	0.54 (0.39–0.74)	**<0.001**
1–49% target dose vs. no therapy	0.71 (0.53–0.95)	**0.021**	0.72 (0.53–0.97)	**0.029**
ACEi/ARB/ARNI use (any dose)	0.59 (0.45–0.74)	**<0.001**	0.74 (0.58–0.95)	**0.017**
ACEi/ARB/ARNI dose ≥50% target dose vs. no therapy or <50% target dose	0.68 (0.50–0.91)	**0.011**	0.79 (0.58–1.08)	0.143
ACEi/ARB/ARNI dose categories				
≥50% target dose vs. no therapy	0.56 (0.41–0.76)	**<0.001**	0.71 (0.51–0.99)	**0.042**
1–49% target dose vs. no therapy	0.61 (0.47–0.79)	**<0.001**	0.76 (0.57–1.01)	0.060
MRA use (any dose)	0.94 (0.75–1.18)	0.628	0.94 (0.74–1.19)	0.590
MRA dose ≥50% target dose vs. no therapy or <50% target dose	0.97 (0.77–1.21)	0.792	0.96 (0.76–1.23)	0.762
MRA dose categories				
≥50% target dose vs. no therapy	0.95 (0.76–1.20)	0.690	0.95 (0.74–1.21)	0.664
1–49% target dose vs. no therapy	0.80 (0.41–1.58)	0.527	0.77 (0.37–1.60)	0.488

Bold values indicate statistical significance.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.
*Adjusted for age, sex, inpatient vs. outpatient status, Heart Failure Association definition of advanced HF, peripheral artery disease, prior stroke or transient ischaemic attack, history of atrial fibrillation, prior myocardial infarction, chronic obstructive pulmonary disease, New York Heart Association class III–IV, systolic blood pressure and estimated glomerular filtration rate (as in the previously published model of the original HELP-HF study).

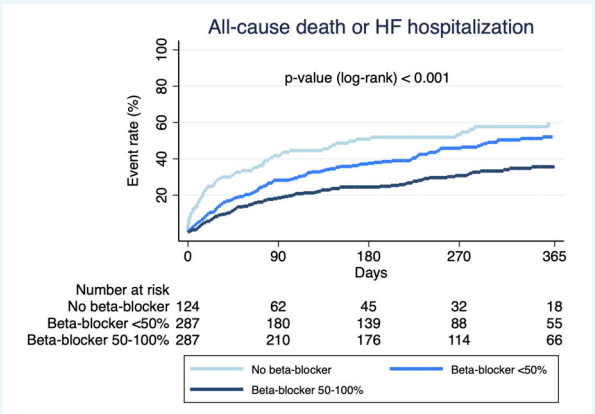


Figure 1 Kaplan–Meier curves for 1-year all-cause death or heart failure (HF) hospitalization according to beta-blocker use and dose (not prescribed vs. prescribed at <50% of the target dose vs. prescribed at ≥50% of the target dose).

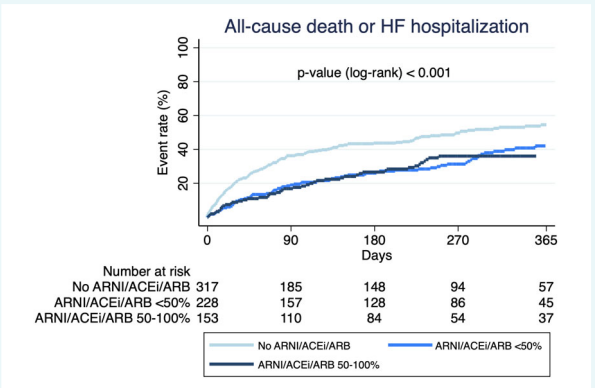


Figure 2 Kaplan–Meier curves for 1-year all-cause death or heart failure (HF) hospitalization according to angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor (ACEi/ARB/ARNI) use and dose (not prescribed vs. prescribed at <50% of the target dose vs. prescribed at ≥50% of the target dose).

and adjusted HR 0.72, 95% CI 0.53–0.97 for those receiving ≥50% and <50% of target doses, respectively). The association between ACEi/ARB/ARNI doses and outcome was not statistically significant at multivariable analysis. Multivariable analyses confirmed that treatment with MRA was not associated with any outcome in this population. Similar results were found when the value of natriuretic peptides was included as a covariate in the multivariable model (online supplementary *Table S4*).

Discussion

To the best of our knowledge, this is the first study investigating use of GDMT in a large population of patients with severe HFrEF. Our study shows that significant gaps remain in prescription and dosing of GDMT in these high-risk patients with at least one marker for advanced HF (*Graphical Abstract*).

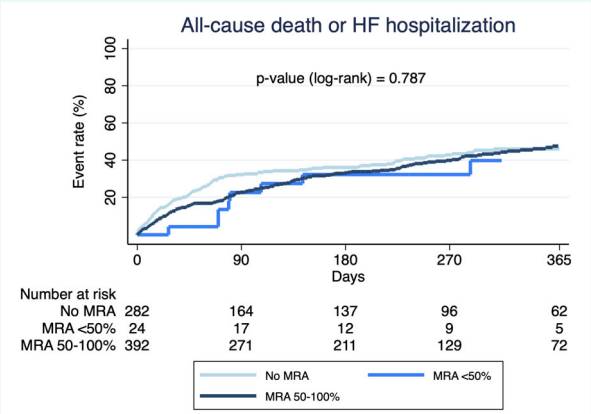


Figure 3 Kaplan–Meier curves for 1-year all-cause death or heart failure (HF) hospitalization according to mineralocorticoid receptor antagonist (MRA) use and dose (not prescribed vs. prescribed at <50% of the target dose vs. prescribed at ≥50% of the target dose).

Overall, 82% of patients received beta-blockers, whereas the prescription of ACEi/ARB/ARNI and MRA was lower (55% and 60%, respectively). Only 69.5% and 34.5% of patients received two and three GDMTs, respectively. The proportion of patients receiving ≥50% of target dose of beta-blockers, ACEi/ARB/ARNI, and MRA was of 41%, 22%, and 56%, respectively. Hypotension, bradycardia, kidney dysfunction and hyperkalaemia were the main reasons for GDMT non-prescription/underdosing. However, GDMT was not prescribed and/or uptitrated for unknown reasons in a meaningful proportion of patients and this might be ascribed to clinical inertia or other patient-related reasons. Markers of severe HF and higher comorbidity burden were among the independent predictors of GDMT non-prescription or lack of achieving ≥50% of target dose. Both the prescription and the administration of a higher dose of beta-blockers were associated with better outcomes. ACEi/ARB/ARNI prescription, regardless of doses, was associated with better outcomes.

Previous registries have described patterns and factors associated with use and dose of HFrEF medications.[6–8,16–19] The CHAMP-HF (Change the Management of Patients with Heart Failure) registry included 3518 outpatients in the United States with chronic HFrEF who did not require heart transplantation, left ventricular assist device, or hospice. Among eligible patients, 67%, 73%, and 33% were prescribed beta-blocker, ACEi/ARB/ARNI, and MRA therapy, respectively. Similar data come from the IMPROVE HF (Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) study, examining dose of GDMT in outpatient clinical practice in United States.[12,20,21] More recently, Stolfo *et al.*[19] reported higher rates of GDMT prescription among 27 430 patients with HFrEF registered in the Swedish HF Registry between 2000 and 2018. In the Swedish HF Registry about 90% of patients received ACEi/ARB/ARNI (17% were on ARNI) and more than 90% received beta-blockers, whereas only 45% were treated with MRA. Notably, the rate of MRA prescription is largely variable in previous reports with, in general, a lower proportion of patients receiving MRA versus other GDMT.[18,19,21–25]

Also, the rates of patients receiving two and three evidence-based medications were low in our population (69.5% and 34.5%). Consistently, in the CHAMP-HF tegistry, among eligible patients only 22% were simultaneously prescribed with ACEi/ARB/ARNI, beta-blocker, and MRA therapy, and 1.1% were simultaneously prescribed with target doses of all three classes of medication.[6] In the CHECK-HF (Chronisch Hartfalen ESC-richtlijn Cardiologische praktijk Kwaliteitsproject HartFalen) registry, including outpatients from the Netherlands, the range for triple therapy largely differed among the different centres, from 16% to 76%.[10] Thus, rates of GDMT prescription in the current analysis are generally in line with previous studies enrolling unselected HFrEF populations.

In our study, only a minority of patients were prescribed with ≥50% of target doses of beta-blockers and ACEi/ARB/ARNI (41.1% and 21.9%, respectively), whereas 56.2% received ≥50% of target dose of MRA. Consistently, in the CHAMP-HF registry, when medications were prescribed, few patients received target doses of beta-blocker (28%), ACEi/ARB (17%) and ARNI (14%), whereas most patients received target doses of MRA therapy (77%).[6] Despite high rates of prescription, underdosing was also common among patients from the Swedish HF Registry. However, the administration of multiple GDMTs was associated with better outcome than the administration of higher doses of less GDMTs.[26]

Although the implementation of GDMT during a hospitalization for acute HF is strongly recommended,[27–30] it may be more challenging due to critical conditions, frailty and/or comorbidities.[31–34] Hypotension and renal dysfunction were among the main reported causes of GDMT underprescription/underdosing.[33] Patients with advanced HF may be less likely to tolerate GDMT because of low cardiac output, hypotension, and severe kidney dysfunction.[3,14] Hypotension was the main cause of lack of tolerance to ARNI also in the LIFE (LCZ696 in Hospitalized Advanced Heart Failure) trial.[35] Indeed, the proportions of patients receiving beta-blockers and ACEi/ARB/ARNI were lower among patients fulfilling the 2018 HFA-ESC criteria for advanced HF, compared with the others. Furthermore, these patients received lower doses of GDMT. These results were consistent with the more severe haemodynamic impairment of these patients.[14] Drugs with a minimal impact on blood pressure (i.e. SGLT2 inhibitors)[36–38] or novel therapies directly targeting left ventricular systolic function without direct effects on blood pressure (i.e. omecamtiv mecarbil)[39,40] may be useful in patients with advanced HF. Similarly, the effects of vericiguat, that recently demonstrated to improve prognosis in a high-risk HFrEF population, should be further investigated in patients with advanced HF.[41,42]

Importantly, no reasons for lack of administration of GDMT were found in a large proportion of patients (ranging from 37% for ACEi/ARB/ARNI to 56% for MRA) and, similarly, no reasons for lack of titration were found in about a half of the cases. Patient-related reasons for not prescribing certain medications including frailty, cognitive impairment, dementia and lack of social and/or familial support as well as unavailability/reimbursement issues could have influenced the decision to not prescribe or

uptitrate GDMT, consistently with what generally considered as clinical inertia.[43,44] Notably, this occurred in patients with severe HF followed up at tertiary care centres where the attention to the implementation of evidence-based treatment should be maximal. Thus, there is still large room for improvement of evidence-based treatment in patients with HFrEF and severe HF.[14]

In multivariable analysis, for each medication class, several patient characteristics were independently associated with lack of HF medication prescription and with the prescription of a dose <50% of the target dose. The predictors of GDMT non-prescription or underdosing are generally in line with other studies, including coexisting COPD for beta-blockers and severe renal dysfunction for ACEi/ARB/ARNI and MRA.[22] Importantly, a large analysis form the Swedish HF Registry showed the safety of continuing MRA treatment in patients with HFrEF and severe CKD.[45] Reasons for the limited adoption of established prognostic therapies in patients with HFrEF have been largely investigated in stable ambulatory patients with HF. Ouwerkerk *et al.*[8] described determinants and clinical outcomes associated with GDMT uptitration among patients with HFrEF from 69 centres in 11 European countries enrolled in the BIOSTAT-CHF study. The BIOSTAT-CHF was specifically designed to prospectively investigate optimization with initiation and uptitration of GDMT in patients with HFrEF, who were enrolled for a recent worsening HF event and suboptimal medical therapy. On the other hand, we performed a retrospective real-world study, without influencing physicians' prescription. Furthermore, we described factors associated with underdosing and underprescription of GDMT in the specific setting of patients with at least one marker of severe HF according to the 'I NEED HELP' criteria and including patients fulfilling the 2018 HFA-ESC criteria for advanced HF. Thus, our study analyses reasons for underprescription of GDMT, including clinical inertia, in the specific setting of patients with markers of HF severity but without any episode of acute decompensation as a reason for enrolment. In this high-risk population, markers of severe HF (e.g. cardiogenic shock at presentation) resulted as independent predictors of GDMT non-prescription/underdosing.

Our study also confirmed that beta-blocker and ACEi/ARB/ARNI use was independently associated with a lower risk of the composite endpoint of death or HF hospitalization and a lower risk of all-cause mortality. Higher doses of beta-blockers were further associated with better prognosis consistently with previous findings,[8,46–49] whereas statistical significance was not reached for ACEi/ARB/ARNI dosing. On one hand, our results confirmed that even small doses of ACEi/ARB/ARNI are associated with better outcomes compared with lack of their administration.[8,26,46,50] D'Amario *et al.*[26] showed that a dual drug approach with renin–angiotensin system inhibitors or ARNI with a beta-blocker at a dose 50–99% of target dose was associated with a 14% lower adjusted risk of cardiovascular death or HF hospitalization compared with monotherapy at a dose ≥100% of target dose. These findings support the initiation of multiple drugs prior to uptitrating each one as recommended in the 2021 ESC guidelines on HF.[1,51] However, our results differ from those of randomized controlled trials directly comparing low versus high doses and from analyses of prospective observational studies showing better outcome with higher doses of ACEi/ARB compared with lower ones.[8,52–55] More recently, the STRONG-HF trial comparing a high-intensity treatment regimen, leading to higher rates of use and of target doses achievement of GDMT, with usual care might support these findings.[27]

These differences may be partially explained by sex as men had better outcomes when receiving 100% of the recommended dose of ACEi or ARBs whereas women had the lowest risk at only 50% of the recommended doses with no further decrease in risk at higher doses in previous studies.[56] However, our data may also be influenced by the relatively small number of patients. The insufficient number of patients enrolled may be a likely reason also for the lack of statistical significance of the relationship between MRA prescription and outcome.

Limitations

Several limitations should be acknowledged. The main limitation of our study is represented by its retrospective nature, with all the limitations associated with this design, for example residual confounding. Second, we evaluated GDMT use at a single time-point, so changes over time, namely initiation, uptitration, downtitration or discontinuation, might occur but were not recorded. This is of utmost importance since some patients had *de novo* HF or were hospitalized due to acute HF, increasing the probability of medication adjustments during follow-up. Third, although different study sites were chosen to increase representativeness, data reflect patients from four high-volume Italian HF centres and thus may not be generalizable to all care practices. Fourth, due to the timing of data collection and the recent approval of SGLT2 inhibitors as an HF drug in Italy, we did not evaluate SGLT2 inhibitor prescription.

Conclusion

In a large, contemporary, real-world population of patients with severe HFrEF, prescription and doses of beta-blockers, ACEi/ARB/ARNI and MRA remain low. Treatment with beta-blockers and ACEi/ARB/ARNI but not MRA was independently associated with outcome. Several factors were associated with the likelihood of GDMT prescription. Future large-scale dedicated studies are needed to further explore the use and prognostic impact of GDMT in this difficult-to-treat and high-risk population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: D.T. reports speaker fees and honoraria from Boehringer Ingelheim, Alnylam and Pfizer, outside the submitted work. M.P. reports personal fees from Abbott Laboratories, AstraZeneca, Boehringer Ingelheim and Vifor Pharma, all outside the submitted work. D.S. reports personal fees from Novartis, Merck, GSK and Acceleron, all outside the submitted work. M.A. reports speaker fees from Abbott Vascular and Medtronic. M. Merlo reports personal fees for congresses from Novartis, Vifor Pharma, Pfizer, and unrestricted research grant from Pfizer,

all outside the submitted work. G.S. reports grants and personal fees from Vifor, Boehringer Ingelheim, AstraZeneca, Novartis, Cytokinetics, Pharmacosmos, personal fees from Medtronic, Servier, TEVA, Edwards Lifescience, INTAS, grants from Boston Scientific, Merck, Bayer, outside the submitted work. M. Metra reports personal consulting honoraria of minimal amount from Abbott, Amgen, Bayer, Edwards Therapeutics, LivaNova and Vifor Pharma for participation in advisory board meetings and executive committees of clinical trials. All other authors have nothing to disclose.

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