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Implementation of guideline-directed medical therapy among patients with acute heart failure admitted to cardiac rehabilitation: the PROMETEO registry

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ABSTRACT

Background and aims: To provide a contemporary description of patients referred to cardiac rehabilitation (CR) in Italy after hospitalization for acute heart failure (HF), focusing on the use and optimization of guideline-directed medical therapy (GDMT) across the spectrum of left-ventricular ejection fraction (LVEF).
Methods: PROMETEO is a prospective, multicentre Italian registry enrolling consecutive adult patients admitted to CR after acute HF. Patients were stratified as HFrEF (LVEF <40%) or HFmrEF/HFpEF (LVEF ≥40%).
Results: Among 263 patients with available LVEF, median age was 68.7 years, 21.7% were female, and 74.9% had HFrEF. Compared with HFmrEF/HFpEF, HFrEF were younger, less frequently female and with higher NT-proBNP levels. At CR admission, 72.1% of HFrEF patients received ACEi/ARB/ARNI, 91.9% beta-blockers, 79.2% MRAs, and 66.0% SGLT2 inhibitors, with a median GDMT score of 6 (IQR 4–8). At discharge, ARNI use increased significantly (58.9%) and the median GDMT score increased to 7 (IQR 4–8; $p = 0.013$), alongside higher beta-blocker dosing and reduced loop diuretic use. Chronic kidney disease and higher baseline GDMT score were negatively associated with GDMT optimization, while higher BMI showed a positive association. In HFmrEF/HFpEF patients, SGLT2 inhibitor use increased from 28.8% to 47.0% ($p = 0.010$), with a concomitant reduction in loop diuretic prescription and dose.
Conclusion: Patients referred to CR after acute HF are mainly male with HFrEF and show substantial comorbidity and treatment complexity. Residential CR represents a key opportunity for GDMT optimization across the HF spectrum.

1. Introduction

Heart failure (HF) is a global pandemic with a high and still increasing prevalence and poses a significant burden on healthcare worldwide [1]. Patients with HF are at high risk of recurrent rehospitalization, clinical deterioration, adverse events, loss of functional capacity, and poor quality of life [1]. Advances in guideline-directed medical therapy (GDMT) have provided significant benefits to the prognosis of patients with HF, especially those with a reduced ejection fraction (HFrEF). However, hospitalization and mortality rates remain high [2].

Cardiac rehabilitation (CR) is a multidisciplinary intervention that includes physical, behavioural, and psychological interventions and has provided consistent achievements in improving cardiovascular prognosis and quality of life across different settings, including HF [3,4]. Exercise has a class I recommendation in all patients with HF who are able to do it, while supervised CR should be considered, especially in those who are frail and/or with comorbidities or severe disease [5]. CR has long been recognized, with recent evidence further emphasizing, as a potential strategy to improve GDMT prescription rates, but limited

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evidence is available [6]. Nevertheless, there is still a large gap in optimal patient referral, uptake, and programme completion rates [7]. Moreover, rehabilitation programmes widely differ between countries, due to legislation and reimbursement rules, with CR not covered in patients with HF with preserved ejection fraction (HFpEF) in the United States [7,8]. Therefore, considering the evolving epidemiological context of HF, we designed a prospective, multi-centre registry to provide continuous information on CR performance. In this study, we describe the characteristics of patients included in the registry, as well as the role of CR in the implementation of GDMT.

2. Methods

2.1. Study design and population

The PROspective MulticEnter registry in patients with acutely dEcompensated heart failure admitted to cardiac rehabilitatiOn (PROMETEO) is an Italian, prospective, multi-centre, registry. It includes consecutive adult patients evaluated between 12 May 2023 and 30 June 2025 at three CR facilities (IRCCS Fondazione Don Gnocchi, Milan; Cardiovascular Rehabilitation Unit, Crema; Cardiovascular Rehabilitation Unit, San Raffaele Scientific Institute) after a recent hospitalization for acute HF. Patients were excluded if not able to sign an informed consent. Cardiac rehabilitation consisted of a structured residential programme lasting approximately 3 weeks, including daily supervised exercise sessions, clinical reassessment, and optimization of medical therapy. The exercise program was delivered according to the patients' hemodynamic status and GDMT titration, with patients classified in four main phenotypes [from A ("All on board and stable") to D ("Deterioration")]. The details of the program and classification are reported in Fig. 1. Given the inpatient setting, adherence to the programme was consistently high. In the present report, patients were stratified according to left-ventricular ejection fraction (LVEF) and excluded if LVEF was missing.

2.2. Study aim

The primary report of the registry aims to provide an updated epidemiological picture of patients referred to residential CR in Italy after a hospitalization for acute HF, in line with the primary aim of the registry, and to focus on the use of GDMT, its management combined with physical exercise during the CR pathway and its implementation at discharge.

2.3. Data collection

Pseudo-anonymised individual patient data on medical history, clinical presentation, echocardiography and laboratory findings, exercise capacity, and medical therapy were collected at baseline and discharge. Clinical outcomes were collected by means of medical records or telephone contact at 6 months after discharge and will be explored in further analyses.

2.4. Left-ventricular ejection fraction

LVEF was defined based on the value at admission to CR or at

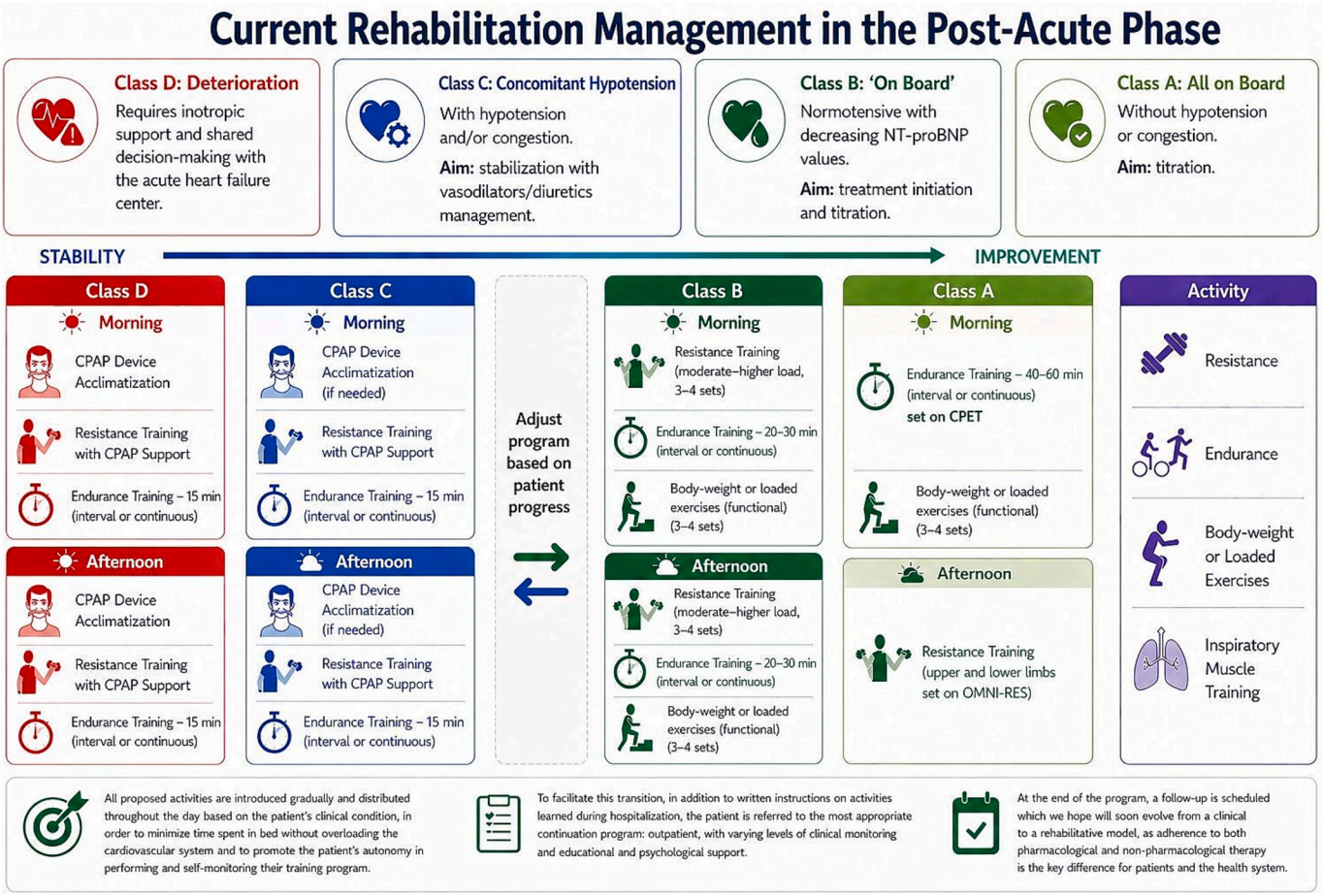

Fig. 1. Exercise prescription in heart failure patients early admitted in cardiac rehabilitation. CPAP: Continuous Positive Airway Pressure; CPET: Cardiopulmonary Exercise Test.

discharge from hospitalization for acute HF. Patients were classified as HFrEF if LVEF was <40%, while patients with LVEF >40% were jointly classified as HFmrEF/HFpEF, as in other reports. [9,10]

2.5. Guideline-directed medical therapy

GDMT classes examined were (1) beta-blockers (BB), (2) angiotensin-converting enzyme-inhibitors (ACEi), angiotensin II receptor blockers (ARB), or angiotensin receptor/neprilysin inhibitors (ARNI) that were mutually exclusive, (3) mineralocorticoid receptor antagonists (MRA), and (4) sodium-glucose cotransport 2 inhibitors (SGLT2i) in patients with HFrEF [5]. Among patients treated, drug dosing was classified into <25%, 25%–49%, 50%–74%, and > 75% of target doses for ACE/ARB, BB, and MRA, according to European Scoiety of Cardiology (ESC) guideline recommendations. [5] Percentages of target doses were not calculated for SGLT2i and ARNI, based on available doses and previous evidence [11]. A modified GDMT score was also calculated in patients with HFrEF, considering only drugs included among GDMT and ranging from 0 to 8 **(Supplementary Table 1)** [11]. SGLT2i were considered the only GDMT recommended in patients with HFmrEF/HFpEF, based on class I recommendations from current HF guidelines [12]. In patients treated with loop diuretics, doses were reported as oral furosemide equivalents (oral torasemide 10 mg = intravenous furosemide 10 mg = oral furosemide 20 mg) [13].

2.6. Ethical statement

The study was approved by the ethics committee of San Raffaele Hospital on 14 December 2022 (number D.30.OSR_PNRR-MAD-2022-12,376,159) and at all sites, and complied with the Declaration of Helsinki. All patients provided written informed consent.

2.7. Statistical analysis

Continuous variables were reported as median and interquartile range (IQR), while categorical variables were recorded as frequencies and percentages. Between-group comparisons were conducted using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables, with Fisher's exact test applied when at least one expected count was less than 5. The Wilcoxon signed-rank test and McNemar's test were used for within-group comparisons of changes in medical therapy from baseline to discharge, as appropriate. A multivariable general linear regression model was built to evaluate the association between variables deemed clinically relevant and increase in the modified GDMT score from admission to discharge. Data were calculated based on non-missing values. All reported *p*-values were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using R software.

3. Results

3.1. Baseline characteristics

Of 289 included subjects, 263 had available data on LVEF and were included in the present analysis. As reported in Table 1, median age was 68.7 (58.5–76.9) years, 31.4% were older than 75 years and 21.7% were female. Median LVEF was 32% (26%–39.5%). Overall, 197 (74.9%) patients were categorized as HFrEF and 66 (25.1%) as HFmrEF/HFpEF. Patients with HFrEF were younger (67.2 [57.2–75.6] years vs 74 [63.3–82.3] years, $p = 0.001$) and less frequently female (17.35% vs 34.8%, $p = 0.005$). History of ischaemic heart disease was less frequent in HFrEF patients and it was identified as the primary aetiology of HF in a lower percentage of patients, despite still being the most common one (43.4% vs 58.5%, $p < 0.001$). HFrEF patients had higher NT-proBNP levels, more cardiac implantable electronic devices (CIED), less valvular prostheses, larger LV dimensions and higher prevalence of

Table 1
Baseline characteristics across the heart failure spectrum.

	Overall	HFrEF	HFmrEF/ HFpEF	
	***N* = 263**	***n* = 197 (74.9%)**	***n* = 66 (25.1%)**	p-value*
Age, years	68.72 [58.49, 76.86]	67.24 [57.16, 75.63]	74.00 [63.25, 82.32]	*0.001*
Age > 75 years	82 (31.4)	52 (26.4)	30 (46.9)	*0.003*
Female sex	57 (21.7)	34 (17.3)	23 (34.8)	0.005
BMI	24.78 [21.63, 27.74]	24.81 [22.18, 27.66]	24.44 [20.99, 29.32]	0.621
Acute phase duration (days)	16.00 [11.00, 26.00]	17.00 [12.00, 24.50]	15.00 [10.00, 28.00]	0.500
Acute care facility type				*<0.001*
Cardiology	224 (85.8)	179 (91.3)	45 (69.2)	
Internal medicine	9 (3.4)	2 (1.0)	7 (10.8)	
Cardiac surgery	17 (6.5)	8 (4.1)	9 (13.8)	
Other	11 (4.2)	7 (3.6)	4 (6.2)	
Comorbidities				
Ischaemic heart disease	147 (55.9)	101 (51.3)	46 (69.7)	*0.010*
Vasculopathy	25 (9.5)	24 (12.2)	1 (1.5)	*0.007*
AF	41 (15.6)	28 (14.2)	13 (19.7)	0.327
TIA / Stroke	20 (7.6)	16 (8.1)	4 (6.1)	0.790
COPD	37 (14.1)	25 (12.7)	12 (18.2)	0.307
CKD	69 (26.2)	52 (26.4)	17 (25.8)	0.999
Anaemia	19 (7.2)	12 (6.1)	7 (10.6)	0.270
Liver disease	13 (4.9)	9 (4.6)	4 (6.1)	0.743
Cognitive impairment	32 (12.2)	24 (12.2)	8 (12.1)	0.999
Musculoskeletal disorder	46 (17.5)	31 (15.7)	15 (22.7)	0.196
Hypertension	144 (54.8)	107 (54.3)	37 (56.1)	0.887
Dyslipidemia	95 (36.1)	72 (36.5)	23 (34.8)	0.883
Diabetes mellitus	82 (31.2)	59 (29.9)	23 (34.8)	0.539
Smoking	130 (49.4)	100 (50.8)	30 (45.5)	0.480
Weight loss	52 (25.2)	40 (25.8)	12 (23.5)	0.853
Falls	9 (4.4)	7 (4.5)	2 (3.9)	0.999
Impaired activities of daily living	100 (49.3)	73 (47.7)	27 (54.0)	0.515
Impaired balance	35 (17.5)	24 (16.0)	11 (22.0)	0.390
Lives alone / no social support	21 (10.3)	15 (9.8)	6 (12.0)	0.605
HF history				
De novo HF	166 (63.1)	120 (60.9)	46 (69.7)	0.239
Primary aetiology				*<0.001*
Coronary artery disease	123 (47.1)	85 (43.4)	38 (58.5)	
Idiopathic cardiomyopathy	87 (33.3)	84 (42.9)	3 (4.6)	
Valvular heart disease	32 (12.3)	15 (7.7)	17 (26.2)	
Infectious diseases	5 (1.9)	2 (1.0)	3 (4.6)	
Infiltrative / storage diseases / endomyocardial diseases	5 (1.9)	4 (2.0)	1 (1.5)	
Drug-induced	3 (1.1)	3 (1.5)	0 (0.0)	
Arrhythmia	3 (1.1)	1 (0.5)	2 (3.1)	
Hypertension	1 (0.4)	0 (0.0)	1 (1.5)	
Metabolic diseases	1 (0.4)	1 (0.5)	0 (0.0)	
Congenital heart disease	1 (0.4)	1 (0.5)	0 (0.0)	
CIED				*0.003*
None	197 (75.5)	140 (71.8)	57 (86.4)	
PM	9 (3.4)	5 (2.6)	4 (6.1)	
ICD	31 (11.9)	27 (13.8)	4 (6.1)	
CRT-P	2 (0.8)	1 (0.5)	1 (0.5)	
CRT-D	20 (7.7)	20 (10.3)	0 (0.0)	
Other	2 (0.8)	2 (1.0)	0 (0.0)	
Valvular prosthesis				*0.019*

(*continued on next page*)

Table 1 (*continued*)

	Overall	HFrEF	HFmrEF/ HFpEF	
None	205 (84.7)	161 (88.5)	44 (73.3)	
Aortic	16 (6.6)	8 (4.4)	8 (13.3)	
Mitral	13 (5.4)	9 (4.9)	4 (6.7)	
Aortic + mitral	8 (3.3)	4 (2.2)	4 (6.7)	
NYHA class, n (%)				0.666
I / II	149 (72.0)	114 (71.3)	35 (74.5)	
III / IV	58 (28.0)	46 (28.8)	12 (25.5)	
SBP, mmHg	105.00 [95.00, 120.00]	100.00 [95.00, 115.00]	117.00 [110.00, 130.00]	*<0.001*
DBP, mmHg	65.00 [60.00, 70.00]	65.00 [60.00, 70.00]	70.00 [60.00, 70.00]	0.072
NTproBNP, pg/mL	1914.00 [789.00, 3774.00]	1986.50 [808.00, 4109.00]	1616.00 [638.00, 3069.00]	0.055
LVEF, %	32.00 [26.00, 39.50]	30.00 [25.00, 34.00]	48.00 [43.00, 54.75]	*<0.001*
EDV, ml	79.60 [66.37, 99.00]	86.00 [76.00, 105.39]	57.00 [49.75, 67.25]	*<0.001*
E/e' ratio	10.00 [8.00, 14.00]	11.00 [8.38, 15.00]	8.35 [7.00, 12.00]	*0.007*
Moderate-to-severe MR	78 (32.8)	67 (37.4)	11 (18.6)	0.010
sPAP, mmHg	35.00 [28.00, 43.00]	35.00 [27.75, 42.25]	34.50 [28.50, 47.25]	0.353
Laboratory tests				
Haemoglobin, g/dL	11.90 [10.53, 13.60]	12.00 [10.60, 13.70]	11.45 [10.20, 12.70]	*0.036*
Total cholesterol, mg/dL	120.00 [99.75, 151.00]	123.00 [100.50, 153.50]	112.00 [96.00, 145.00]	0.157
LDL, mg/dL	62.00 [46.00, 88.00]	65.00 [47.00, 92.25]	55.00 [43.00, 81.00]	0.076
Triglycerides, mg/dL	104.50 [82.75, 135.25]	103.00 [79.50, 130.00]	115.00 [91.00, 144.00]	0.057
eGFR, ml/min/1.73 mq	60.79 [42.59, 78.56]	62.79 [42.59, 80.39]	57.17 [42.55, 74.25]	0.228
Transferrin saturation, %	28.00 [16.00, 173.00]	27.00 [16.00, 151.50]	36.58 [18.75, 192.00]	0.115
Ferritin, ng/mL	220.00 [117.70, 395.05]	210.80 [118.72, 381.25]	259.60 [112.00, 439.00]	0.661
Scales				
Barthel Index	90.00 [77.00, 95.00]	90.00 [80.00, 95.00]	87.50 [66.25, 95.00]	0.611
RCS-E	12.00 [11.00, 13.00]	12.00 [10.00, 13.00]	12.00 [11.00, 13.00]	0.606
Functional parameters				
Peak VO2, ml/kg/min	14.39 [12.10, 16.09]	14.47 [12.70, 16.02]	13.17 [10.62, 16.16]	0.539
Peak VO2, % predicted	56.70 [46.25, 66.88]	52.10 [44.85, 65.65]	66.60 [55.07, 83.00]	*0.019*
VE/VCO2 slope	41.44 [35.88, 47.12]	41.00 [35.05, 46.35]	45.80 [39.50, 49.30]	0.222
VO2/work rate	9.00 [7.57, 9.94]	9.00 [7.66, 10.07]	9.14 [7.49, 9.40]	0.613
30-Second Sit-to-Stand Test score	9.00 [0.00, 12.00]	9.00 [0.00, 11.75]	8.00 [0.00, 11.50]	0.961
6-Minute Walk Test distance, metres	293.50 [160.00, 395.00]	305.50 [177.00, 398.75]	259.00 [113.25, 349.25]	0.125
6-Minute Walk Test, % predicted	59.50 [42.80, 74.40]	58.50 [41.50, 74.40]	63.00 [47.75, 74.50]	0.398

Table values are n (%) or median [interquartile range];
AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT—P, cardiac resynchronization therapy with pacemaker; CRT—D, cardiac resynchronization therapy with defibrillator; DBP, diastolic blood pressure; EDV, end-diastolic volume; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; RCS-E, Rehabilitation Complexity Scale-Extended; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; TIA, transient ischemic attack; VE/VCO_2 slope, ventilatory efficiency (minute ventilation to carbon dioxide production slope); VO_2, oxygen consumption. * *The missing value for each variable have been reported in Supplemental Table 4.*
* p-values from Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables, with Fisher's exact test applied when at least one expected count was less than 5; p-values <0.05 are italicised.

moderate-to-severe mitral regurgitation. Chronic kidney disease was similar between groups, as were frailty assessment scales and functional capacity, which significantly improved at discharge **(Supplementary Table 2)**.

3.2. Medical therapy at admission

At admission, as shown in Table 2 and Figs. 2 and 3, in the HFrEF group, 27.4%, 44.7%, 91.9%, 79.2%, and 66% of patients were treated with ACE/ARB, ARNI, BB, MRA, and SGLT2i, respectively. Overall, 72.1% were treated with ACE/ARB/ARNI. The median dose of ACE/ARB, BB, and MRA were 12%, 25%, and 100% of target doses, respectively. Single, double, triple, and quadruple therapy were prescribed in 8.1%, 15.2%, 32%, and 43.7% of patients with HFrEF, respectively **(**Fig. 4**)**. The median GDMT score was 6 (4–8, **Supplementary Fig. 1**). Loop diuretics were prescribed in 76.1% of HFrEF patients with a median dose of 35 (25–75) mg of furosemide equivalents.

At admission, as shown in Table 2 and Fig. 2, in the HFmrEF/HFpEF group, 28.8% of patients were treated with SGLT2i. In addition, 43.9%, 15.2%, 71.2%, and 56.1% of patients were treated with ACE/ARB, ARNI, BB, and MRA, respectively (Fig. 2). Overall, 59.1% were treated with ACE/ARB/ARNI. Loop diuretics were prescribed in 74.2% of patients with a median dose of 50 (25–50) mg of furosemide equivalents.

3.3. Changes in medical therapy at discharge

At discharge, as shown in Table 2 and Figs. 2 and 3**,** in the HFrEF group, 16.8%, 58.9%, 91.4%, 72.1%, and 71.6% of patients were treated with ACE/ARB, ARNI, BB, MRA, and SGLT2i, respectively. Overall, 75.7% were treated with ACE/ARB/ARNI. The median dose of ACE/ARB, BB, and MRA were 12%, 38%, and 50% of target doses, respectively. Single, double, triple, and quadruple therapy were prescribed in 5.6%, 15.2%, 29.9%, and 46.2% of patients with HFrEF, respectively

Table 2
Pharmacological treatment and GDMT implementation stratified by LVEF.

	Overall, n = 263			HFrEF, n = 197 (74.9%)			HFmrEF/HFpEF, n = 66 (25.1%)		
	Admission	Discharge	p-value*	Admission	Discharge	p-value*	Admission	Discharge	p-value*
ACE / ARB	83 (31.6)	65 (24.7)	*0.034*	54 (27.4)	33 (16.8)	*0.004*	29 (43.9)	32 (48.5)	0.628
ACE / ARB - % of maximum dose	0.12 [0.12, 0.25]	0.12 [0.06, 0.25]	0.843	0.12 [0.12, 0.25]	0.12 [0.06, 0.14]	*0.033*	0.25 [0.12, 0.25]	0.25 [0.12, 0.50]	0.11
ARNI	98 (37.3)	128 (48.7)	*<0.001*	88 (44.7)	116 (58.9)	*<0.001*	10 (15.2)	12 (18.2)	0.724
BB	228 (86.7)	233 (88.6)	0.532	181 (91.9)	180 (91.4)	0.999	47 (71.2)	53 (80.3)	0.211
BB - % of maximum dose	0.25 [0.12, 0.50]	0.35 [0.25, 0.50]	*0.015*	0.25 [0.12, 0.50]	0.38 [0.25, 0.50]	*0.032*	0.25 [0.12, 0.38]	0.25 [0.12, 0.50]	0.346
MRA	193 (73.4)	171 (65.0)	*0.016*	156 (79.2)	142 (72.1)	0.061	37 (56.1)	29 (43.9)	0.186
MRA - % of maximum dose	1.00 [0.50, 1.00]	0.50 [0.50, 1.00]	*0.001*	1.00 [0.50, 1.00]	0.50 [0.50, 1.00]	*0.002*	1.00 [0.50, 1.00]	0.62 [0.50, 1.00]	0.670
SGLT2 inhibitor	149 (56.7)	172 (65.4)	*0.004*	130 (66.0)	141 (71.6)	0.118	19 (28.8)	31 (47.0)	*0.010*
Loop diuretic	199 (75.7)	153 (58.2)	*<0.001*	150 (76.1)	116 (58.9)	*<0.001*	49 (74.2)	37 (56.1)	*0.019*
Furosemide equivalents	40.00 [25.00, 50.00]	25.00 [25.00, 50.00]	*<0.001*	35.00 [25.00, 75.00]	25.00 [25.00, 50.00]	*<0.001*	50.00 [25.00, 50.00]	25.00 [25.00, 50.00]	*0.032*
Ivabradine	12 (4.6)	11 (4.2)	0.999	11 (5.6)	9 (4.6)	0.724	1 (1.5)	2 (3.0)	0.999
Digitalis	7 (2.7)	9 (3.4)	0.752	5 (2.5)	7 (3.6)	0.683	2 (3.0)	2 (3.0)	0.999
Antiarrhythmic drugs	68 (25.9)	67 (25.5)	0.999	54 (27.4)	56 (28.4)	0.850	14 (21.2)	11 (16.7)	0.546
Statin	186 (70.7)	189 (71.9)	0.755	143 (72.6)	142 (72.1)	0.999	43 (65.2)	47 (71.2)	0.343
Ezetimibe	99 (37.6)	134 (51.0)	*<0.001*	73 (37.1)	103 (52.3)	*<0.001*	26 (39.4)	31 (47.0)	0.131
Antithrombotic agents	219 (83.3)	223 (84.8)	0.596	165 (83.8)	163 (82.7)	0.831	54 (81.8)	60 (90.9)	0.114
GLP-1 receptor agonists	9 (3.4)	15 (5.7)	0.211	7 (3.6)	8 (4.1)	0.999	2 (3.0)	7 (10.6)	0.074
Number of GDMT classes			0.589			0.414			0.545
0	8 (3.0)	9 (3.4)		2 (1.0)	6 (3.0)		6 (9.1)	3 (4.5)	
1	30 (11.4)	22 (8.4)		16 (8.1)	11 (5.6)		14 (21.2)	11 (16.7)	
2	48 (18.3)	50 (19.0)		30 (15.2)	30 (15.2)		18 (27.3)	20 (30.3)	
3	83 (31.6)	81 (30.8)		63 (32.0)	59 (29.9)		20 (30.3)	22 (33.3)	
4	94 (35.7)	101 (38.4)		86 (43.7)	91 (46.2)		8 (12.1)	10 (15.2)	
GDMT score	–	–		6.00 [4.00, 8.00]	7.00 [4.00, 8.00]	*0.013*	–	–	

Table values are n (%) or median [interquartile range]; p-values <0.05 are italicised. *p-values from Wilcoxon signed-rank test and McNemar's test; p-values <0.05 are italicised.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium–glucose cotransporter 2; GLP-1, glucagon-like peptide 1; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

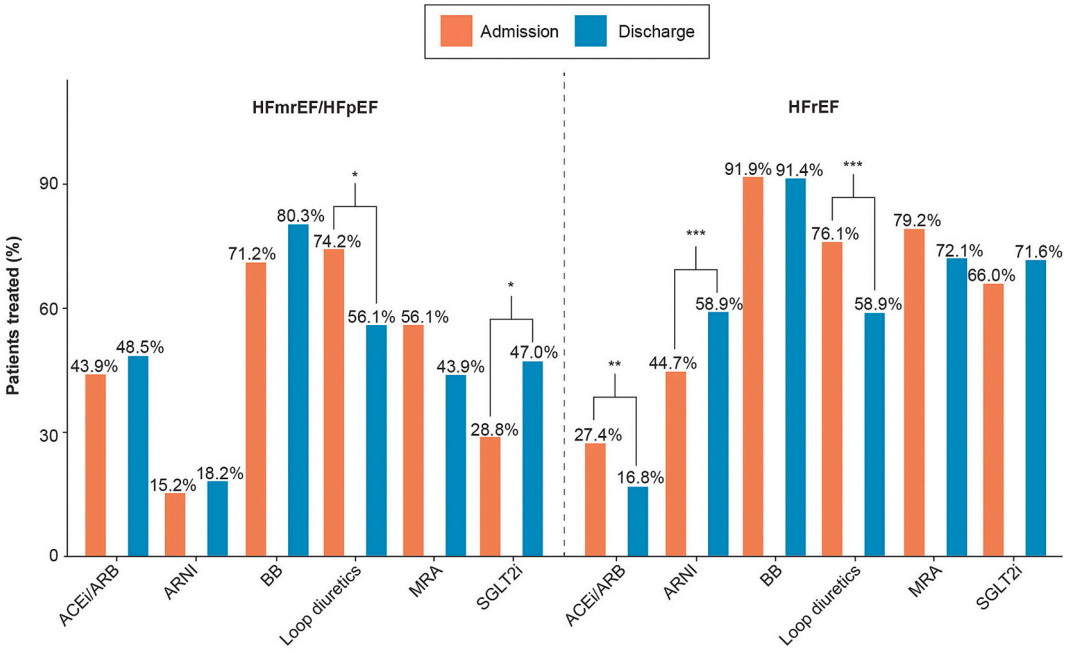

Fig. 2. Proportion of patients treated with each drug class at admission and discharge across the HF spectrum. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

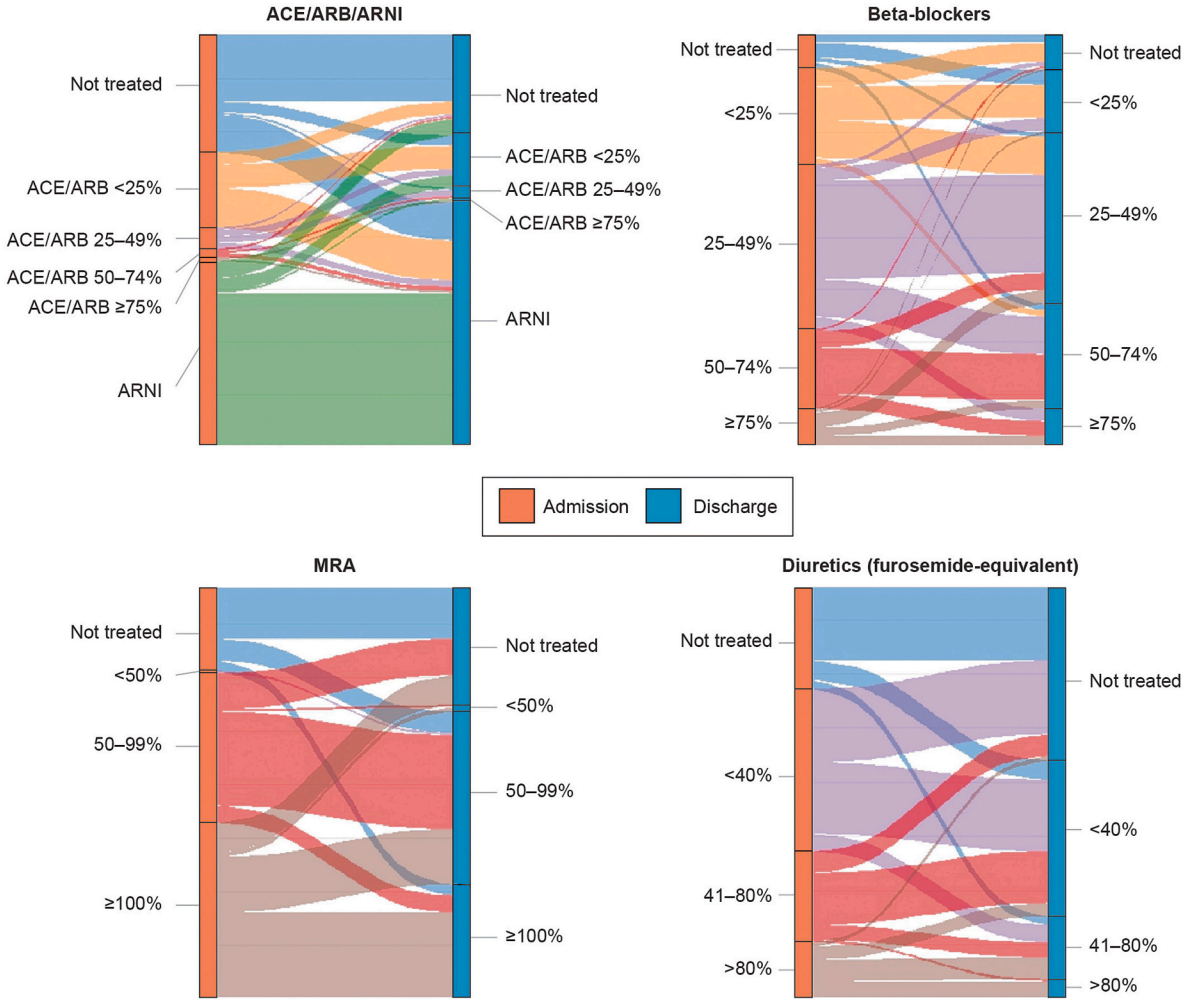

Fig. 3. GDMT implementation from admission to discharge. Sankey diagrams showing the proportion of patients treated with different doses of GDMT drugs and loop diuretics in patients with HFrEF at admission and discharge. SGLT2i are not shown as they are available only at 100% of target dose for HFrEF patients. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; SGL2i, sodium-glucose cotransporter-2 inhibitors.

(Fig. 4). The median GDMT score was 7 (4–8, **Supplementary Fig. 1**). Loop diuretics were prescribed in 58.9% of patients with HFrEF with a median dose of 25 (25–50) mg of furosemide equivalents. With respect to admission, patients were less frequently treated with ACE/ARB and more frequently treated with ARNI ($p < 0.001$), while a numerical increase was found for SGLT2i prescription. A significant increase in the median dose of BB ($p = 0.032$) and GDMT score ($p = 0.013$) was found at discharge, while the median dose of MRA ($p = 0.002$) and of loop diuretics ($p < 0.001$) decreased significantly. Variables found to be negatively associated with increase in the GDMT score from admission to discharge were history of chronic kidney disease (CKD) and a higher GDMT score at baseline, while higher body mass index (BMI) was positively associated with GDMT optimization (**Supplementary Table 3**).

At discharge, as shown in Table 2 and Fig. 2**,** in the HFmrEF/HFpEF group, 47% of patients were treated with SGLT2i, with a significant increase compared with admission ($p = 0.010$). In addition, 48.5%, 18.2%, 80.3%, and 43.9% of patients were treated with ACE/ARB, ARNI, BB, and MRA, respectively. Overall, 66.7% were treated with ACE/ARB/ARNI. Loop diuretics were prescribed in 56.1% of patients with a median dose of 25 (25–50) mg of furosemide equivalents and a significant decrease both in prescription rate and doses with respect to admission ($p = 0.019$ and $p = 0.032$). Guidelines-directed therapy was managed with a concomitant approach of tailored exercise programme adapted to the patient's phenotype as reported in Fig. 1.

4. Discussion

The present study provides a real-world snapshot of the contemporary population referred to CR at three Italian centres after a hospitalization for acute HF. Our findings underscore critical aspects in the characterization of these patients and in the optimization of GDMT from admission to discharge **(Graphical Abstract)**.

4.1. Epidemiology and demographics

HF represents a major healthcare burden with high costs and negative prognosis [1]. Beside improvements in GDMT implementation, other measures are required to reduce the overall risk of patients with HF, especially in the post-acute setting. CR is a multidisciplinary intervention that includes, but is not limited to, exercise training. Despite the cost-effectiveness of CR, it remains underutilized, with only a minority of patients receiving CR in Europe and the United States [14,15]. Data on these patients are scant and not updated, and tend to focus on exercise training only. In addition, most available registries report data on CR across the spectrum of cardiovascular disease, updated before the latest HF guidelines [12,14]. Furthermore, they do not take into account the multidisciplinary role provided by CR, which includes the titration

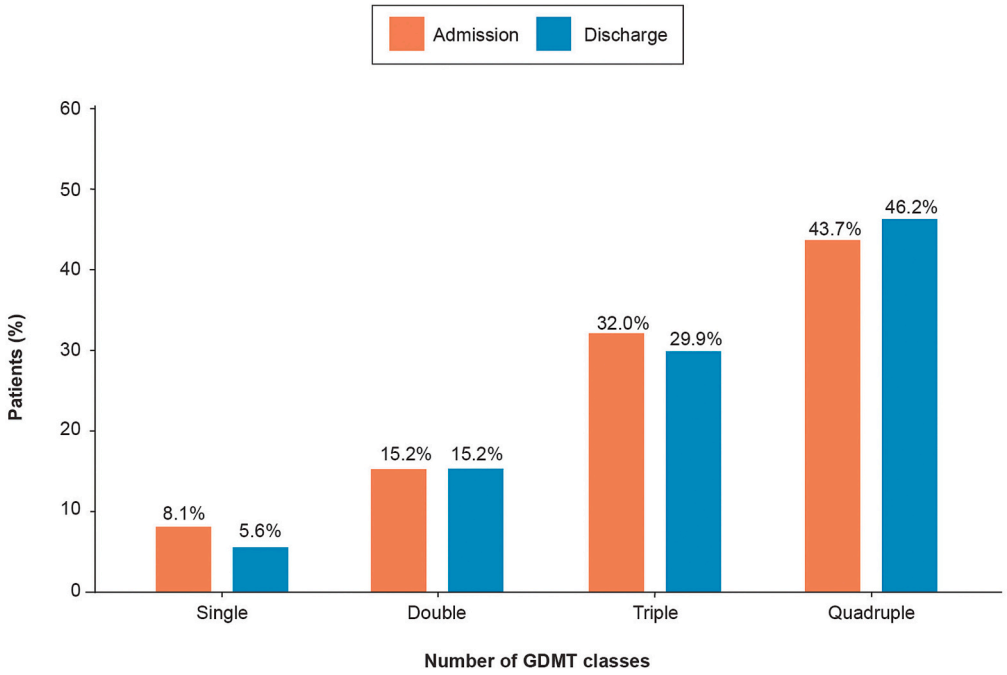

Fig. 4. Proportion of HFrEF patients treated with combinations of GDMT at admission and discharge. Bar chart showing the proportion of HFrEF patients treated with single, double, triple or quadruple GDMT at admission and discharge. GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction.

of medical therapy that can more appropriately occur when medical treatment is combined with exercise.

In our contemporary registry, patients referred to CR after a hospitalization for acute HF were predominantly male. This reflects historical lower referral and adherence bias towards women and CR, which still persists [16]. The worldwide trend of male predominance among patients with HF (71% among patients with HFrEF in the Swedish HF registry, 76% in the contemporary Italian BRING-UP-3 HF study) only partially explains such discrepancies, with lack of gender-tailored CR programmes and lower perceived benefit potentially contributing [17–19].

Overall, our cohort had a median age of 68.7 years, with less than one-third older than 75 years. Although older than reported in previous registries and trials on CR [14,20], our cohort reflects the overall epidemiology of HF in Italy, as well as the possibility of referring older patients to intensive CR, overcoming potential age-related biases [18]. Approximately half of the population presented classical cardiovascular risk factors (e.g. hypertension and/or dyslipidaemia), with the overall comorbidity burden lower than reported in other HF registries [21,22]. A possible explanation resides in the referral pathway, since most patients were discharged from cardiology wards, where patients tend to be younger, more frequently ischaemic, and with HFrEF [23].

High Barthel index values, limited prevalence of other frailty domains, and moderate rehabilitation complexity characterized our cohort. Although this might suggest our population to be of low complexity, it is likely that these tools may not adequately capture the true complexity of patients with HF referred to CR. Standard scales may underestimate disease-specific limitations, including haemodynamic instability, reduced exercise tolerance, and the need for close medical supervision and therapy optimization, highlighting a potential mismatch between currently used assessment tools and the clinical needs of this population. This implies a changing paradigm that should be updated by policymakers with particular reference to the metrics adopted to evaluate the inpatient CR time and the specific needs of these patients – presently, only 3 weeks of residential CR is funded in Italy and this is insufficient. Despite the well-known difficulty in assessing frailty in HF patients, with the need of a more complete and holistic evaluation and and with limitations related to the use and interpretation of classical physical mobility assessments, significant improvements in physical and psychological parameters were found after CR, highlighting its role in multi-domain risk mitigation after a hospitalization for acute HF [21,24]. Whether CR centres represent the ideal environment to develop specific frailty assessment for HF patients remains to be elucidated.

4.2. *Implementation of GDMT in HFrEF*

GDMT implementation to reduce the risk associated with the post-acute period represents a fundamental therapeutic strategy to be implemented [12]. Recent data demonstrated how rapid up-titration of GDMT is feasible and protective in patients with HF, and CR may help in achieving this [25]. Our population of HFrEF patients, who remain the predominant phenotype, showed suboptimal prescription of some class I-recommended drugs, especially ARNI, at admission. Conversely, prescription rates for BB were high and in line with recent reports, while SGLT2i and MRA demonstrated even broader uptake than usual, likely reflecting improved awareness of the benefit of these drugs [26,27]. At discharge, prescription rates substantially increased for ARNI, paralleled by a decrease in ACE/ARB prescription, reflecting a proactive transition towards a superior foundational therapy (Fig. 2). A numerical increase was also seen for SGLT2i and a slight decrease for MRA, although neither were significant. Concomitant changes in diuretic therapy, further discussed below, may contribute to justify these data. Moreover, only a minority of patients received target doses of the drugs and less than 50% were on quadruple therapy both at admission and discharge, falling short of other recent national data where better implementation was found at follow-up [28]. However, such discrepancies are potentially linked to different patient profiles, with those discharged after acute HF and referred to CR potentially frailer in terms of cardiovascular stability, thus impacting GDMT tolerability [21]. Similar rates were found in the recent IMPLEMENT-HF study, with 44.8% of HFrEF patients discharged on quadruple medical therapy after a hospitalization for HF, supporting such interpretation [29]. Consistently, our data confirm better GDMT implementation with respect to historical registry data, likely reflecting contemporary HF care after widespread adoption of guidelines updates

and recommendations on GDMT use [30–32].

When using a comprehensive evaluation for GDMT prescription, most patients demonstrated high levels of the modified GDMT score, likely reflecting physicians prioritizing initiation of multiple drugs rather than up-titration, as this provides additional benefits to long-term outcomes [33]. The GDMT score also significantly increased from admission to discharge, with the majority having a score ≥ 7 out of 8, highlighting the importance of alternative strategies to evaluate GDMT uptake, as well as the potential impact of a structured CR programme in optimizing HF care.

Despite overall improvement, full GDMT optimization remained limited. This likely reflects multiple factors, including residual clinical instability following acute HF, renal dysfunction, and concerns regarding adverse events such as hyperkalaemia, particularly when combining multiple neurohormonal agents. This is supported by the evidence of CKD as the most significant parameter limiting GDMT optimization, as previously demonstrated, being a potential contraindication for most of the recommended drugs and increasing the risk of hyperkalaemia [34]. Similarly, the observed reduction in MRA prescription and dosing may therefore represent a safety-driven adjustment rather than true de-escalation. In addition, although CR provides a structured environment to overcome therapeutic inertia, it cannot be completely excluded. These findings highlight the challenges of translating guideline-recommended target doses into real-world post-acute populations.

4.3. GDMT in HFmrEF/HFpEF

Regarding GDMT for HFmrEF and HFpEF, SGLT2i are still the only drugs with a class I recommendation in the ESC guidelines [12]. Overall, lower prescription rates than for HFrEF patients were found both at admission and discharge. Lower awareness of the more recent indications for SGLTi in this subset of patients, as well as more extensive comorbidity burden, might explain such findings. However, the role of therapeutic inertia in the underprescription of these drugs could not be excluded, with less than 50% receiving an SGLT2i at discharge [35,36]. Nevertheless, prescription significantly improved during CR, confirming the trend seen in the HFrEF population and the potential role of CR in GDMT optimization. Prescription rates of all other HFrEF GDMT drugs demonstrated a nonsignificant increase from admission to discharge, likely reflecting the heterogeneity of the HFmrEF/HFpEF population, as also seen in previous studies [9,10,37]. These data might appear to contrast with guideline recommendations and recent evidence, especially regarding the use of BB, although in line with recent HFpEF trials, where high prescription rates of BB were found [9,10,37]. However, concomitant indications, such as arrhythmias, and the need to control cardiovascular risk factors might also explain such an increase, with CR providing the opportunity to correct additional therapeutic targets during its course, as demonstrated also by better implementation of lipid-lowering therapies.

4.4. Diuretic management

Over the course of CR, prescription rates and doses of loop diuretics significantly decreased, irrespective of LVEF. Loop diuretics remain a cornerstone of HF therapy, especially in the acute setting, as congestion is a primary driver of adverse outcomes [38]. However, loop diuretics per se do not act on remodelling, have inconsistent impact on long-term outcomes, and should be used at the lowest dose possible [39]. Recent evidence demonstrated that optimization of GDMT might allow for improvement in congestion status and decrease in loop diuretics, providing substantial benefits for patients with HF [40,41]. Concomitant increase in SGLT2i, as well as in ARNI prescription, seen in our registry might therefore explain such findings. However, reduction in loop diuretics might also be a driver for the concomitant reduction in the doses of MRA prescribed in patients with HFrEF, as they help to control hyperkalaemia [42]. Nevertheless, prescription rates remained higher than in other cohorts, with most patients being on at least half of the MRA target dose [26].

4.5. Limitations

The PROMETO registry has some limitations that need to be acknowledged for appropriate interpretation. Firstly, despite being a multicentre registry, the limited number of centres included potentially limits the external generalizability of our findings. Additionally, the enrolled cohort was predominantly male, reflecting a demographic imbalance inherent to the pathology and shared by many other registries, but limiting the applicability of our results to women, with limited data on sex-specific patterns in therapeutic approaches, outcomes, or responses to therapy. Moreover, given the observational nature of the study and the small sample size, causality could not be inferred, and residual unmeasured variables might still influence the observed results. In addition, absence of data on contraindications and underprescription limit the interpretation of GDMT implementation. Finally, the present analysis does not include clinical outcome data. Nevertheless, this is the first registry detailing an exercise approach combined to uptitration of GDMT in heart failure management in CR.

5. Conclusion

In conclusion, data from the PROMETEO registry demonstrated that, in a contemporary cohort of patients referred to CR after a hospitalization for acute HF, male patients and patients with HFrEF still predominate. CR showed the potential to help optimize HF care, through a balanced exercise programme, especially by reducing disability and increasing GDMT prescription rates, across the EF spectrum. Further data on the long-term impact of such measures are eagerly awaited to further support the role of CR in this high-risk setting. In the meantime, policymaker awareness is needed to maintain a common perspective on the pathway of these patients in order to improve their care, including common prognostic and outcome indicators in the acute and post-acute setting.

CRediT authorship contribution statement

Alessandro Villaschi: Writing – original draft. **Maria Letizia Oreni:** Formal analysis. **Anastasia Toccafondi:** Writing – original draft, Validation, Supervision. **Ignazio Cusmano:** Data curation. **Stefano Gonella:** Data curation. **Riccardo Gonella:** Data curation. **Gaia Coni:** Data curation. **Anna Torri:** Data curation. **Paola Grati:** Data curation. **Marco Ambrosetti:** Writing – review & editing, Validation. **Domenico Cianflone:** Writing – review & editing. **Nuccia Morici:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2026.101962.

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