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RESEARCH ARTICLE

# Medical treatments at 6 months in hospitalized and ambulatory HFrEF patients in the BRING-UP 3 Heart Failure study

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## Abstract

**Introduction** The BRING-UP 3 Heart Failure (HF) study was designed to evaluate the real-world implementation of guideline-directed medical therapy (GDMT) for patients with heart failure with reduced ejection fraction (HFrEF), given the limited evidence on the uptake of the contemporary four-pillar treatment strategy.

**Methods** BRING-UP 3 HF study is an observational, prospective, nationwide investigation encompassing 179 sites. This analysis includes HFrEF patients enrolled in the ambulatory and hospitalized cohorts with complete pharmacological data at 6-month follow-up. The objective was to describe the use of the four GDMT pillars after 6 months.

**Results** Among 3201 HFrEF patients enrolled, 142 (4.4%) had died by 6 months, and treatment data were available for 2950 patients. Mean age was 69 ± 11 years (26.6% > 75 years), 18.0% were female. Prescription rates of GDMT were high at baseline and remained stable over 6-months, with a shift from ACE-I/ARBs to ARNIs, and a modest increase in SGLT2i use. A significant reduction in diuretic prescription was also observed. Quadruple therapy was prescribed in 64.3% of patients at 6 months

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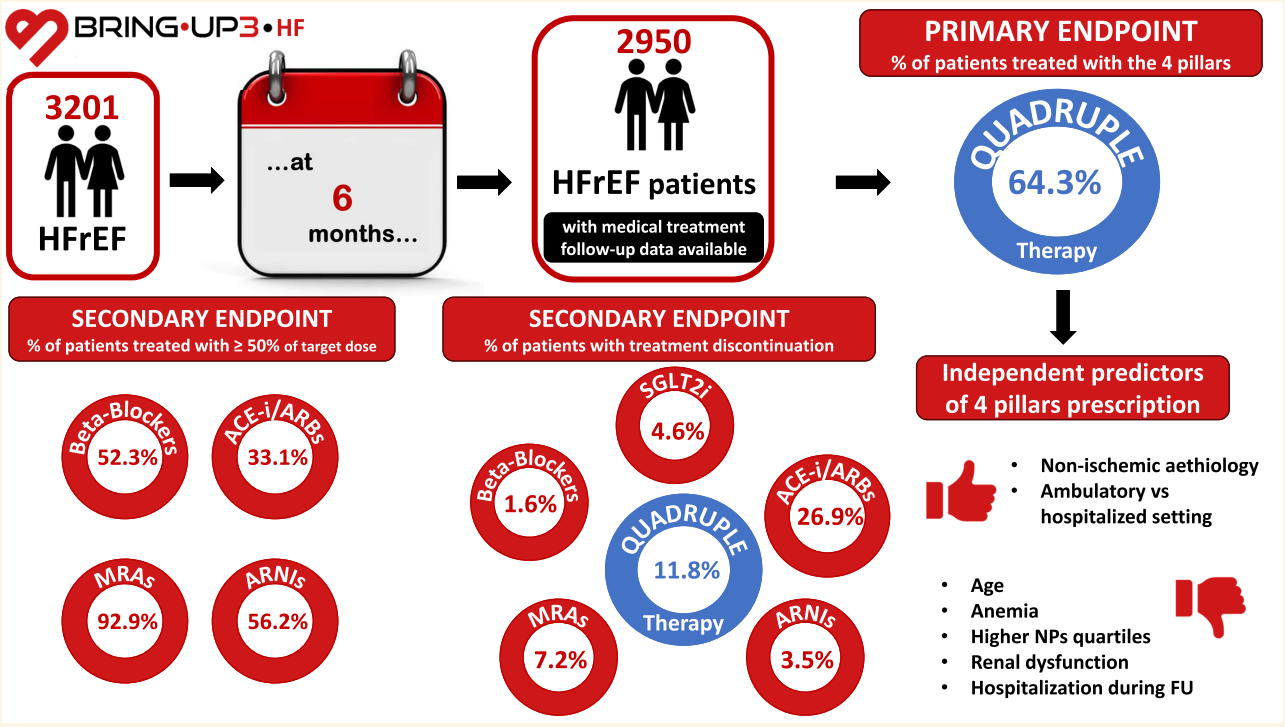
versus 63.9% at baseline/discharge ($P$ = NS), while quadruple therapy including ARNI went from 52.9% to 55.9%, $P < .0001$. Dose up-titration of GDMT remained suboptimal, with most agents prescribed at <50% of target doses. Discontinuation rates at follow-up were very low.

**Conclusion** In this large nationwide cohort, guideline-directed therapies for HFrEF were widely implemented and maintained over 6 months with excellent treatment persistence. However, dose optimization remains a key unmet need in routine clinical practice.

**Graphical Abstract**




Six-month management of heart failure patients enrolled in the BRING-UP 3 HF study

**Keywords** Chronic heart failure • Medical treatments • Adherence • Registry • Guidelines



## Introduction

In patients with HF and reduced ejection fraction (HFrEF), angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) have been shown to improve outcomes when replaced/added to the original background treatments, of a beta-blocker (BB), a renin–angiotensin system blocker (RASI) and a mineralocorticoid receptor antagonist (MRA).[1–3] Therefore, the 2021 ESC guidelines and the 2022 AHA/ACC/HFSA introduced a novel four-pillar therapeutic approach for treating patients with HFrEF, that includes ARBs/ACE-I/ARNI, BBs, MRA, and SGLT2i[4,5] and overcomes the trial-derived stepwise approach in treatment implementation. These guidelines also recommend that most of these treatments should be up-titrated to the target dose (the dose tested in the clinical trials that demonstrated the benefit of these treatments) or, if this is not possible, to the maximum tolerated dose. The STRONG-HF trial[6] showed benefit in patients who received rapid implementation and dose escalation of guideline-recommended treatment. However, translating the results into clinical practice appears to be challenging.[6] Previous observational studies have shown that inertia, comorbidities, prescribing rules and contraindications represent barriers for guideline recommendations implementation,[7–9] but most of these studies were conducted in the past 'three-pillar approach in the pre-SGLT2i era'. The BRING-UP 3 Heart Failure study (BRING-UP 3 HF) was designed as a nationwide initiative to: (i) evaluate the level of guidelines implementation in clinical practice; (ii) address main reasons for the remaining gaps between guidelines and clinical practice. The baseline prescription rates across ejection fraction spectrum of ambulatory patients enrolled in the BRING-UP 3 HF study were recently published showing a high level of adherence to guideline recommendations.[10] Here we describe 6-months follow-up data of HFrEF patients enrolled both in the acute and ambulatory setting of care and we analyze the 6-months prescription rates of the four therapeutic pillars, which represents the primary endpoint of the study.

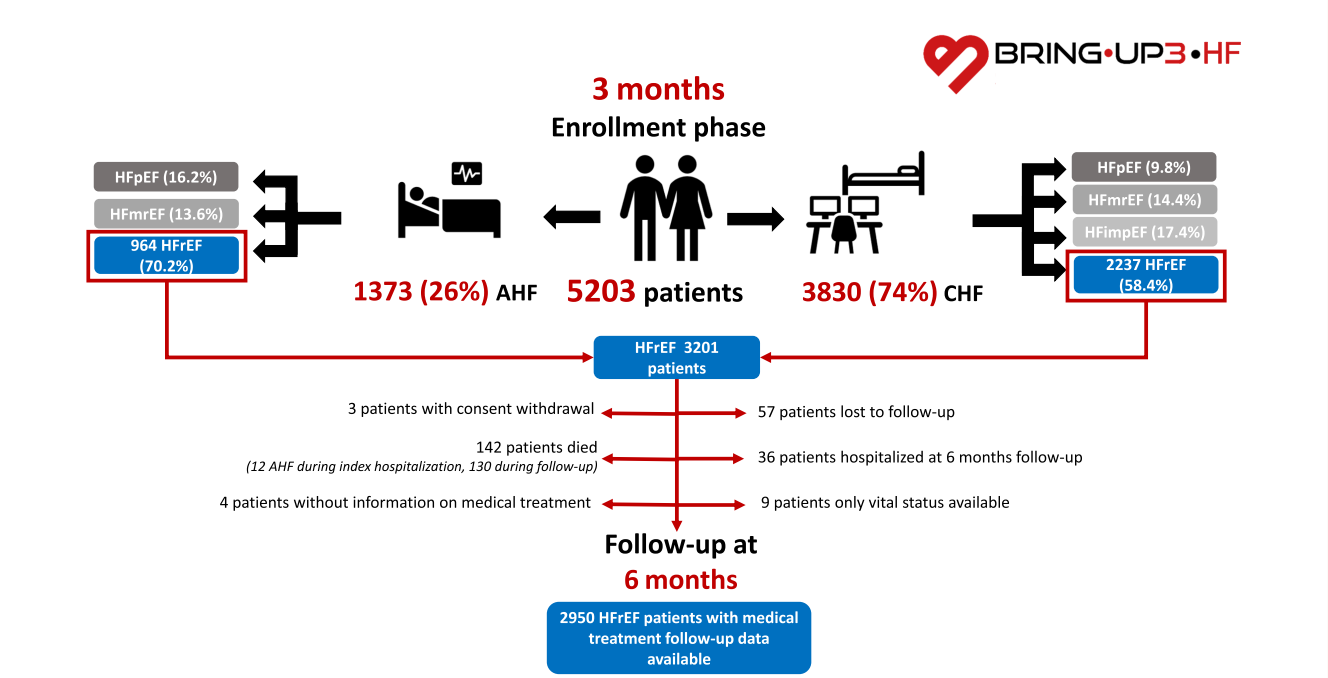



**Figure 1** Study flow-chart and patient selection. AHF, acute heart failure; CHF, chronic heart failure; HFpEF, heart failure with preserved ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFimpEF, heart failure with improved ejection fraction

# Methods

The study design, inclusion criteria, procedures and outcomes have been described in depth elsewhere.[10] Briefly, the BRING-UP 3 HF study is an observational, prospective, multicentre investigation conducted in a large and representative sample of Italian cardiology sites, including both hospitalized and ambulatory HF patients. It is conducted through two 3-months guided patient data collections, each of one preceded by an educational intervention on guideline recommendations. For patients enrolled in both periods, primary and secondary end-point evaluation is scheduled at 6 months.

This paper focuses on HFrEF patients enrolled in both settings of care in the first enrolment phase with pharmacological treatment data available at 6-months follow-up (*Figure 1*). For these patients the primary objective of the study was the rate of four pillars combination at 6-months follow-up. Baseline clinical characteristics of patients treated with or without the four pillars at 6 months and the independent predictors of four pillars prescription at 6-months are reported. Secondary outcomes included a 6-month assessment of tolerability (e.g. discontinuation rates) and the target dose achievement. Patients' clinical outcomes will be analysed over a follow-up period of 12 months and, therefore, are not shown in the present paper.

The study conforms to the principles outlined in the Declaration of Helsinki. The protocol has been approved by ethics committee in accordance with the national regulations. Each patient provided written informed consent to participate in the study.

## Statistical analysis

Categorical variables are presented as percentages or number and percentages and compared using the Chi-square test. Continuous variables are reported as mean and standard deviation (SD), when normally distributed, and compared using the *t*-test. Laboratory examinations are instead reported as median and inter-quartile range (IQR), independently from their distribution, and compared using the Mann–Whitney *U* test. Changes in medical treatments prescriptions are evaluated using the McNemar test.

We compared baseline clinical characteristics, medical treatments, and all-cause hospitalizations at 6 months of patients with or without quadruple therapy at 6 months. Multivariable logistic regression analyses were performed to identify covariates independently associated with quadruple therapy prescription at 6 months, considering those which resulted statistically significant at univariate analysis ($P < .05$). Two models were performed, the first with clinical variables only, and the second with clinical, instrumental and laboratory variables. Finally, a sensitivity analysis was performed including the information on patients hospitalized for any cause during the 6 months follow-up period in the second model. Pharmacological therapy prescribed at baseline was not considered in the multivariable analyses because strongly associated to the end-point of the logistic regression.

A *P*-value of less of .05 was considered statistically significant. All tests were two-sided. The analyses were performed using SAS software, version 9.4.

# Results

As shown in *Figure 1*, at the 6-month follow-up 142 (4.4%) patients had died, 36 patients were currently hospitalized, 3 patients withdrew consent, 4 patients had no information on medical treatment, 9 patients had only vital status available, and 57 patients were lost to follow-up. Therefore, our study population consists of the 2950 patients with available data on medical treatment at the 6-month follow-up visit.

## Medical treatments prescribed at 6-months follow-up

Prescription rates of main medications used for the treatment of heart failure and treatment combinations at discharge/end of baseline visit and at the 6-months follow-up visit are shown in *Figures 2 and 3* respectively. As shown in *Figure 2*, prescription rates for most HF treatments remained stable, with a slight decrease for MRAs and a more significant decrease for ACE-I/ARBs, partly related to a switch to

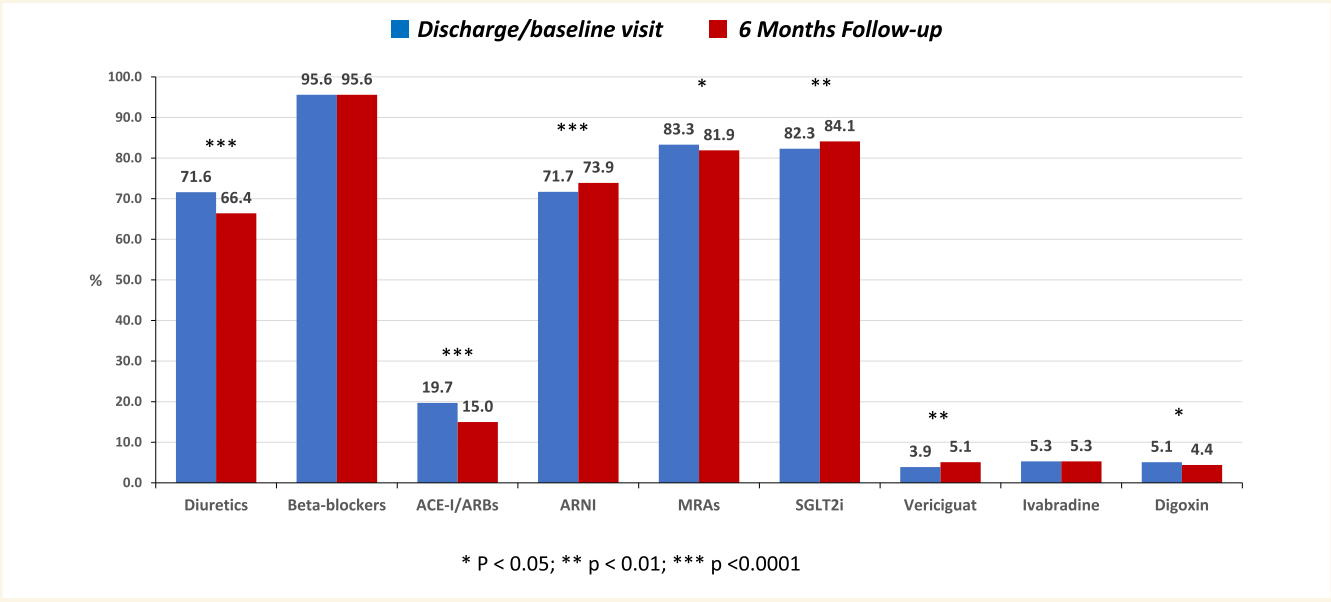



**Figure 2** Heart failure medical treatments prescribed at baseline or at discharge and at 6-months follow-up. ACE-I, ACE-inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; HFrEF, heart failure with reduced ejection fraction; MRA, mineral corticoid antagonists; SGLT2i, Sodium-Glucose-Cotransporter-inhibitors

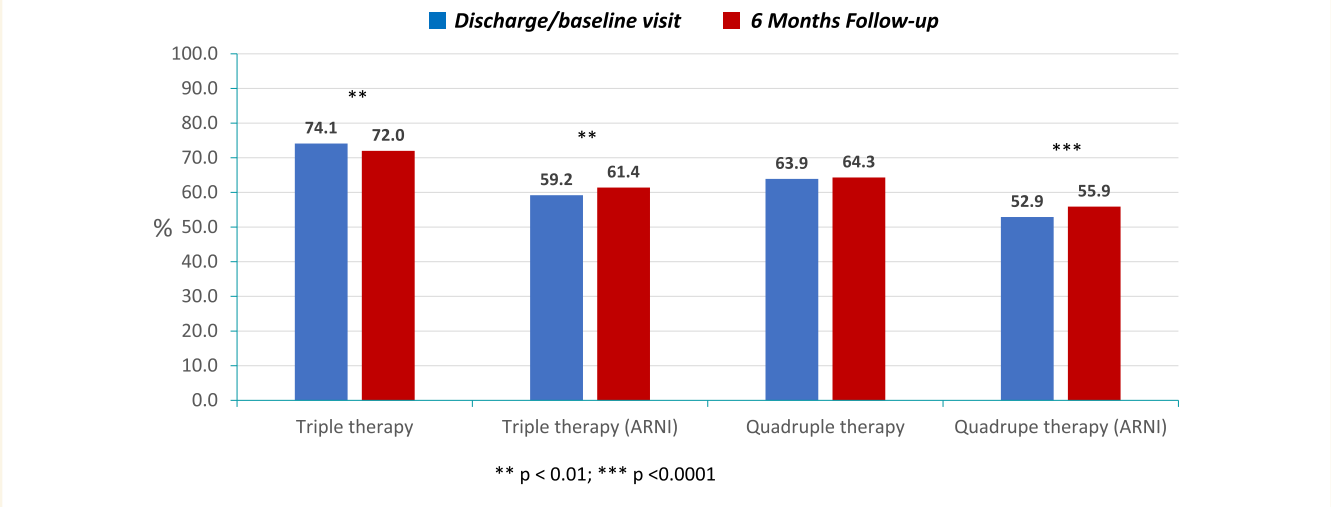



**Figure 3** Guideline recommended treatments combinations at baseline or at discharge and at 6-months follow-up. ARNI, angiotensin receptor neprilysin inhibitors

ARNI, which increased slightly. Also, SGLT2i and, to a minor extent vericiguat, increased at 6 months, while diuretics prescription was reduced to 66.4%, with therefore one third of the patients not taking them. The percentage of patients treated with a combination of the four therapeutic pillars at 6 months was 64.3% (primary endpoint of the study), a percentage similar to the one observed at discharge or at the end of enrolment visit. Quadruple therapy including an ARNI raised to 55.9%. Triple therapy (BB + ACE-I/ARB/ARNI + MRA) had a slight reduction from 74.1 to 72.0%, while triple therapy including an ARNI raised from 59.2 to 61.4%.

Target dose achievement at 6 months was also analysed and compared with baseline rates (*Figure 4*). For most considered treatments (except MRAs) target dose achievement was poor at baseline and did not improve considerably during follow-up. In patients enrolled in the acute setting of care BBs and RASi were prescribed at a dose <50% of target dose in most cases. Prescription of guideline recommended treatments, as well as target dose achievement by gender is reported in Supplementary Figures S1–S3.

*Table 1* shows the discontinuation rate of the components of quadruple therapy at 6 months in the whole study population and according

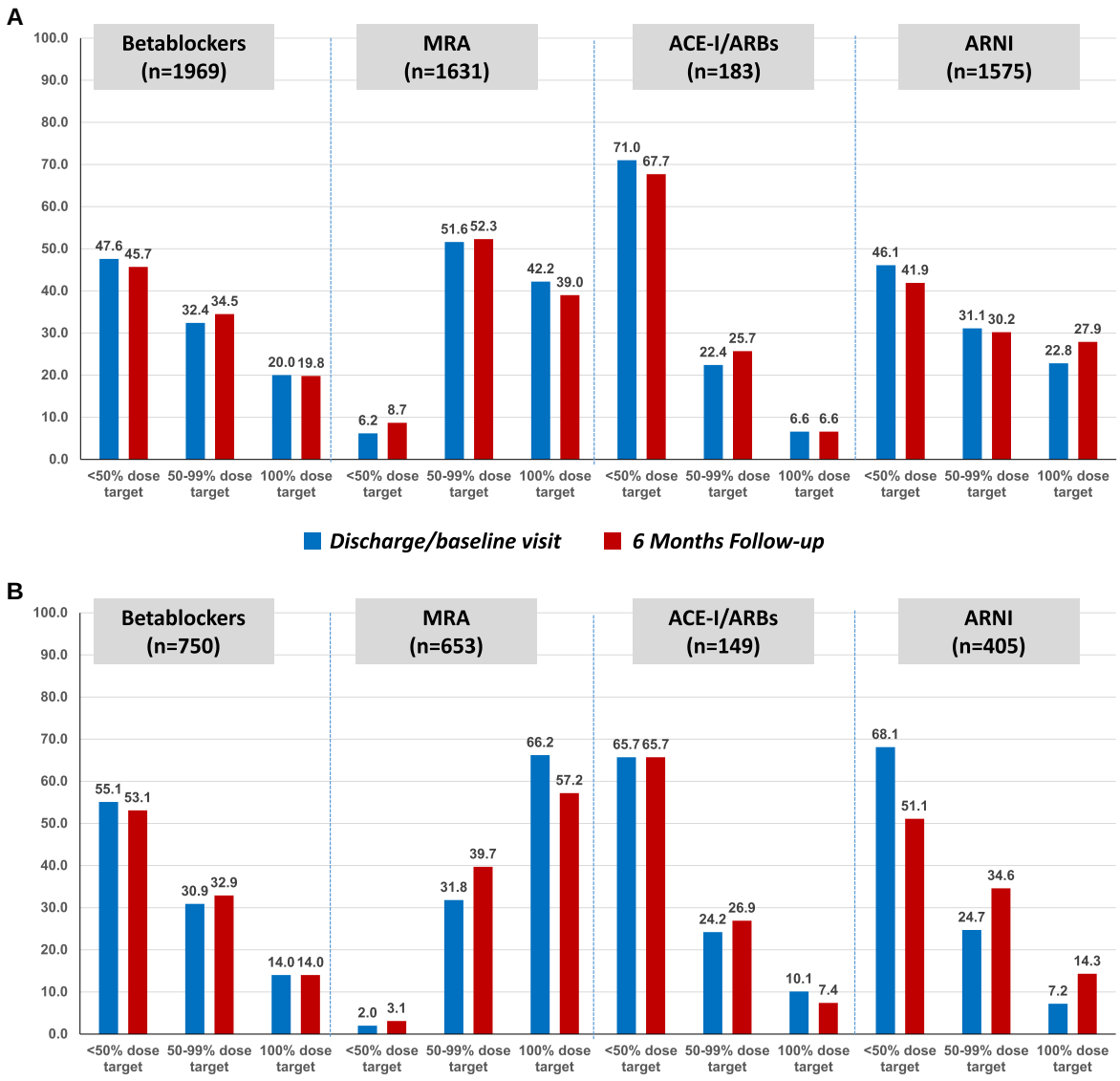



**Figure 4** Target dose achievement at baseline and at 6 months follow-up among patients with both doses available. (*A*) Patients enrolled in the ambulatory setting. (*B*) Patients enrolled in the hospitalized setting

**Table 1 Discontinuation rate of the four pillars in HFrEF patients at 6 months according to setting of enrolment**

| | All (n. 2950) | AHF (n. 837) | CHF (n. 2113) |
|---|---|---|---|
| **Quadruple therapy** | 11.8% (223/1886) | 18.6% (93/500) | 9.4% (130/1386) |
| **Beta-blockers** | 1.6% (44/2819) | 3.4% (27/785) | 0.8% (17/2034) |
| **ACE-I/ARBs** | 26.9% (156/580) | 33.3% (95/285) | 20.7% (61/295) |
| **ARNI** | 3.5% (75/2117) | 6.3% (28/443) | 2.8% (47/1674) |
| **MRA** | 7.2% (176/2456) | 10.1% (73/724) | 6.0% (103/1732) |
| **SGLT2i** | 4.4% (106/2428) | 8.0% (51/636) | 3.1% (55/1792) |

Among the 156 patients suspending ACE-I/ARBs, 96 (61.5%) had been switched to ARNIs at 6 months visit: 34/61 (55.7%) and 62/95 (65.3%) in the ambulatory and in the hospitalization setting of enrolment respectively. Among the 75 patients suspending ARNIs, 28 (37.3%) had been switched to ACE-I/ARBs at 6 months visit: 21/47 (44.7%) and 7/28 (25.0%) in the ambulatory and in the hospitalization setting of enrolment respectively.

ACE-I, ACE-inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitors; MRA, mineral corticoid antagonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

to the enrolment setting of care. The overall discontinuation rate of the quadruple therapy was 11.8% and was higher among patients enrolled during hospitalization (18.6 vs 9.4%). Analysing the single components of quadruple therapy, BBs had the lowest discontinuation rate, followed by ARNIs, SGLT2i, MRAs and ACE-I/ARBs. However, ACE-I/ARBs and ARNIs discontinuation rates were partly related to switch to ARNIs (61.5%) and to ACE-I/ARBs (37.3%) respectively. For all these treatments, withdrawal rates were lower in patients enrolled in the ambulatory setting. Reasons for four pillars non-prescriptions are shown in Supplementary Table S1. Main reasons for BBs non-prescription were bradyarrhythmia and symptomatic hypotension, while symptomatic hypotension and severe renal impairment/worsening renal function were the most common reason for RASi non-prescription. The latter followed by hyperkalaemia was the most frequent reason for MRAs non-prescription. Finally, genitourinary infections and severe renal impairment were the most frequently reported causes for SGLT2i non-prescription.

## Clinical characteristics of patients on quadruple therapy at 6 months

Baseline demographic and clinical characteristics of HFrEF patients according to quadruple prescription at 6 months are shown in Table 2. Although numerically fewer patients from Southern Italy were on quadruple therapy, differences among geographic areas were not statistically significant. Comparing patients with or without quadruple therapy several significant differences could be observed. Those receiving a four pillars combination were younger, more frequently managed in sites with a structured HF clinic, more often enrolled in the ambulatory setting of care. Furthermore, patients on quadruple therapy had less frequently an ischaemic aethiology and several cardiac and non-cardiac comorbidities such as atrial fibrillation, diabetes and moderate renal insufficiency (eGFR <60 mL/min). These patients had more often an implanted device and higher BMI. Moreover, patients on quadruple therapy had lower EF levels, higher mean end diastolic volume and a more preserved

**Table 2 Clinical characteristics and treatments of HFrEF patients treated with or without quadruple therapy at 6 months**

| | All (n. 2950) | Quadruple (n. 1897) | No-Quadruple (n. 1053) | *P* |
|---|---|---|---|---|
| **Geographic area** | | | | .08 |
| **North** | 52.1 | 53.5 | 49.6 | |
| **Centre** | 21.2 | 21.0 | 21.4 | |
| **South** | 26.7 | 25.5 | 29.0 | |
| **HF outpatient clinic, %** | 88.9 | 89.8 | 87.4 | **.046** |
| **N. of pts enrolled by the site, %** | | | | .2818 |
| **<30** | 18.2 | 17.6 | 19.1 | |
| **30** | 38.8 | 38.3 | 39.8 | |
| **>30** | 43.0 | 44.1 | 41.1 | |
| **Age (years), mean ± SD** | 69 ± 11 | 67 ± 11 | 72 ± 11 | **<.0001** |
| **Age >75 years, %** | 32.2 | 26.6 | 42.3 | **<.0001** |
| **Females, %** | 18.0 | 17.5 | 19.1 | .27 |
| **Enrolment setting, %** | | | | **<.0001** |
| **Hospitalized** | 28.4 | 25.7 | 33.1 | |
| **Ambulatory** | 71.6 | 74.3 | 66.9 | |
| **HFH in the 6 months prior to enrolment, %** | 21.9 | 21.9 | 21.8 | .93 |
| ***available for 2851 pts*** | | | | |
| **Ischaemic aethiology, %** | 52.0 | 48.9 | 57.6 | **<.0001** |
| **Hypertension, %** | 67.6 | 66.5 | 69.4 | .22 |
| **Diabetes, %** | 32.8 | 31.6 | 34.9 | **.006** |
| **History of Atrial Fibrillation, %** | 38.0 | 35.7 | 42.1 | **.0002** |
| **Previous stroke, %** | 6.9 | 7.1 | 6.6 | .73 |
| **COPD, %** | 16.3 | 15.5 | 17.9 | .09 |
| ***available for 2851 pts*** | | | | |
| **Device: *CRT-P/CRT-D/ICD*, %** | 45.9 | 47.8 | 42.6 | **.006** |
| **Baseline SBP, mmHg (mean ± SD)** | 120 ± 19 | 120 ± 18 | 121 ± 20 | **.02** |
| **Baseline SBP ≤110 mmHg, %** | 38.9 | 40.5 | 35.8 | **.012** |
| **Baseline DBP, mmHg (mean ± SD)** | 76 ± 11 | 73 ± 11 | 72 ± 11 | .81 |
| **Baseline HR, bpm (mean ± SD)** | 73 ± 17 | 72 ± 17 | 74 ± 18 | .08 |
| **BMI ≥ 27 Kg/m$^2$, %** | 43.1 | 45.1 | 39.4 | **.003** |
| **BMI, kg/m$^2$ (mean ± SD)** | 27.0 ± 4.9 | 27.2 ± 5.1 | 26.6 ± 4.6 | **.0006** |
| **Peripheral oedema, %** | 16.7 | 14.9 | 19.9 | **.0006** |

*Continued*

**Table 2** ***Continued***

| | All (n. 2950) | Quadruple (n. 1897) | No-Quadruple (n. 1053) | *P* |
|---|---|---|---|---|
| **Atrial Fibrillation on ECG, %** | 22.2 | 20.4 | 25.6 | **.001** |
| **LBB, %** | 16.8 | 17.2 | 16.1 | .07 |
| **EF %, (mean ± SD)** | 32.0 ± 6.3 | 31.9 ± 6.2 | 32.3 ± 6.4 | **.04** |
| **EF ≤30%, %** | 41.6 | 42.7 | 39.7 | .11 |
| **EDV mL, (mean ± SD)** | 167.2 ± 63.5 | 170.82 ± 64.9 | 160.5 ± 60.4 | **.0003** |
| ***available for 2080 pts*** | | | | |
| **TAPSE mm, (mean ± SD)** | 18.7 ± 3.9 | 18.9 ± 3.9 | 18.4 ± 3.9 | **.002** |
| ***available for 2248 pts*** | | | | |
| **TAPSE <18 mm, %** | 34.1 | 32.4 | 37.1 | **.02** |
| ***available for 2248 pts*** | | | | |
| **eGFR, ml/min, median [IQR]** | 62.1 [44.9–80.4] | 66.3 [49.9–83.3] | 54.0 [36.7–72.9] | **<.0001** |
| ***available for 2821 pts*** | | | | |
| **eGFR <60 mL/min, %** | 46.4 | 40.1 | 57.6 | **<.0001** |
| ***available for 2821 pts*** | | | | |
| **Creatinine, mg/dL, median [IQR]** | 1.1 [0.9–1.5] | 1.1 [0.9–1.4] | 1.2 [1.0–1.7] | **<.0001** |
| ***available for 2821 pts*** | | | | |
| **Potassium, mEq/L, median [IQR]** | 4.4 [4.0–4.8] | 4.4 [4.0–4.7] | 4.4 [4.0–4.8] | .46 |
| ***available for 2692 pts*** | | | | |
| **Potassium >5 mEq/L, %** | 10.1 | 9.4 | 11.5 | .08 |
| ***available for 2692 pts*** | | | | |
| **Haemoglobin, g/dL, median [IQR]** | 14.0 [12.5–15.0] | 14.1 [13.0–15.3] | 13.3 [12.0–14.8] | **<.0001** |
| ***available for 2757 pts*** | | | | |
| **Haemoglobin <12 g/dL F, <13 M, %** | 26.4 | 20.6 | 36.6 | **<.0001** |
| ***available for 2757 pts*** | | | | |
| **Iron deficiency** (absolute/relative)**, %** | 60.2 | 62.0 | 57.5 | .26 |
| ***evaluable for 601 pts*** | | | | |
| **BNP, pg/ml, median [IQR]** | 511 [195–1102] | 446 [168–1089] | 600 [245–1200] | **.02** |
| ***available for 685 pts*** | | | | |
| **NT-proBNP, pg/mL, median [IQR]** | 1630 [581–4285] | 1271 [496–3340] | 2637 [946–6436] | **<.0001** |
| ***available for 1398 pts*** | | | | |
| ***Treatments prescribed at baseline*** | | | | |
| **ACE-I/ARBs, %** | 19.7 | 16.7 | 25.1 | **<.0001** |
| **ARNIs, %** | 71.8 | 81.8 | 53.7 | **<.0001** |
| **Beta-blockers, %** | 95.6 | 98.7 | 89.9 | **<.0001** |
| **MRAs, %** | 83.3 | 95.3 | 61.5 | **<.0001** |
| **SGLT2i, %** | 82.3 | 93.7 | 61.7 | **<.0001** |
| **Diuretic treatment, %** | 71.6 | 68.7 | 76.8 | **<.0001** |
| **Diuretic treatment, %** | | | | **<.0001** |
| **No** | 28.4 | 31.3 | 23.2 | |
| **Yes** | 50.9 | 49.5 | 53.4 | |
| **Yes, potentiated** | 20.7 | 19.2 | 23.4 | |
| **Triple therapy, %** | 74.1 | 92.5 | 41.0 | **<.0001** |
| **Quadruple therapy, %** | 63.9 | 87.0 | 22.3 | **<.0001** |
| ***Hospitalizations during 6 months follow-up*** | | | | |
| **All hospitalizations, %** | 17.7 | 15.1 | 22.2 | **<.0001** |
| **Urgent cardiac hospitalization, %** | 10.5 | 7.4 | 16.1 | **<.0001** |
| ***Cardiological visits during 6 months follow-up***[a] | | | | |
| **At least one visit performed, %** | 36.0 | 35.8 | 36.3 | .78 |

Significant *P* values in bold.
[a]Other than the one scheduled at 6 months follow-up.

**Table 3 Independent predictors of Quadruple Therapy at 6 months**

| | Model I<br>Clinical variables<br>*P*<br>OR [95% CI] | Model II<br>Clinical and instrumental variables<br>*P*<br>OR [95% CI] |
|---|---|---|
| **Clinical variables** | | |
| **Age (years)** | *P* < .0001<br>0.96 [0.96–0.97] | *P* < .0001<br>0.97 [0.97–0.98] |
| **Female gender** | NS | NS |
| **Enrolment setting** | *P* = .002 | *P* = .0184 |
| **Ambulatory vs hospitalized** | 1.36 [1.12–1.66] | 1.30 [1.05–1.62] |
| **HF Ambulatory** | NS | NS |
| **Ischaemic aethiology** | *P* < .0001<br>0.71 [0.61–0.84] | *P* = .0003<br>0.77 [0.65–0.92] |
| **Diabetes** | NS | NS |
| **Device: *CRT-P/CRT-D/ICD*** | NS | NS |
| **Baseline SBP, mmHg** | NS | NS |
| **BMI, Kg/m$^2$** | NS | NS |
| **Peripheral oedema** | NS | NS |
| **Instrumental and laboratory variables** | | |
| **History of AF/Atrial Fibrillation on ECG** | | NS |
| **EF % ≤ 25 vs >30** | | NS |
| **(25–30] vs >30** | | |
| **TAPSE mm,** | | NS |
| **<18 vs ≥18** | | |
| **unknown vs ≥18** | | |
| **Creatinine** | | *P* < .0001 |
| **>1.5 vs ≤1.5** | | 0.44 [0.36–0.54] |
| **Unknown vs ≤1.5** | | 0.91 [0.53–1.56] |
| **Anemia**[a] | | *P* < 0.0001 |
| **Yes vs No** | | 0.62 [0.51–0.75] |
| **Unknown vs No** | | 1.01 [0.65–1.58] |
| **BNP/NT-proBNP** | | *P* < .0001 |
| **First tertile vs third tertile** | | 1.32 [1.01–1.73] |
| **Second tertile vs third tertile** | | 1.28 [0.99–1.65] |
| **Unknown vs third tertile** | | 0.81 [0.64–1.03] |

The following variables were inserted in the logistic models [when more than two categories were present, dummy variables were introduced to define a reference group (RG)]: Clinical parameters at baseline: age (continuous), gender, enrolment setting, HF ambulatory, ischaemic aethiology, diabetes, implanted device, SBP (continuous), BMI (continuous), peripheral oedema. Instrumental and laboratory parameters at baseline: history of AF/atrial fibrillation on ECG, EF [≤25%; (25–30%); >30% (RG) ], TAPSE [<18 mm; ≥18 mm (RG); unknown], creatinine [≤1.5 (RG); >1.5; unknown], anaemia [no (RG); yes; unknown)], BNP/NT pro BNP [first tertile; second tertile; third tertile (RG), unknown]

AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CI, confidence interval; CRT, Cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; OR, odds ratio; TAPSE, Tricuspid Annular Plane Systolic Excursion.

[a]Males Hb < 13 g/dl, Females Hb < 12 g/dl, at baseline.

right ventricular function. Several differences in blood test results were observed, with quadruple therapy patients having higher haemoglobin levels, less hyperkalaemia (>5 mEq/L) and lower natriuretic peptide levels. Interestingly, iron deficiency, which had been evaluated in only one fifth of the population, was highly prevalent (~60%) but did not differ among patients with or without quadruple therapy at 6 months. Additionally, as expected, patients on quadruple therapy were more frequently prescribed at baseline on ARNI than on ACE-I/ARBs, had higher prescription rates of BBs, MRAs and SGLT2i and lower prescription rates of diuretics. Finally, patients receiving quadruple therapy at 6-months follow-up less frequently were hospitalized during the follow-up. *Table 3* shows the independent predictors of quadruple therapy at 6 months. After adjustment for the clinical characteristics, younger age, outpatient setting of care, and non-ischaemic aethiology resulted significantly associated to a higher quadruple therapy prescription at 6 months; adding instrumental and laboratory exams to the model also lower creatinine and natriuretic peptide levels and the absence of anaemia were associated with a higher prescription of quadruple therapy. Finally, when a sensitivity analysis was performed adding to the second model the information on incident hospitalizations during the 6 months, the results were consistent with the previous two models, and the incident hospitalizations were associated to a lower probability of quadruple therapy prescription at 6 months [OR 0.62, 95% CI (0.57–0.89), *P* = .0007].

# Discussion

European and US guidelines have recently introduced new treatments recommendations and a new therapeutic approach for patients with HF.[4,5] BRING-UP 3 HF is one of the first studies to focus on the contemporary management of patients with HF in a large and representative sample of Italian cardiology sites. The present analysis aims to describe treatment variations at 6-months follow-up in the 2950 HFrEF patients enrolled in the acute and ambulatory settings during the first enrolment phase of the study. The most relevant findings of the 6 months follow-up are shown in the *Graphical Abstract* and can be summarized as follows:

- Prescription rates for the four therapeutic pillars recommended by current guidelines, which were already high at the end of the baseline visit or at discharge, remained stable at 6 months (~65%).
- Dose up-titration during the 6-months follow-up was limited, with only a minority of the patients achieving the target doses and a high percentage of patients was still treated with <50% of target doses.
- Discontinuation rates were overall quite low (~12%), but they were almost double in patients enrolled in the acute setting compared with those included as outpatients.
- Most of the causes for non-prescription of the four pillars at 6 months were the expected reported reasons and justify 'real' non-prescription, while some reasons (e.g. hyperkalaemia, clinical stability) require a further cultural effort to narrow the gap between guideline recommendations and clinical practice.
- Independent predictors of quadruple therapy prescription at 6 months include demographic (younger age) and enrolment setting related factors, non-ischaemic aethiology, absence of comorbidities (renal insufficiency and anaemia) and indicators of severity (higher natriuretic peptides values and incident hospitalizations).

The new paradigm for the medical treatment of patients with HFrEF introduced by the most recent HF guidelines needed to be confirmed in the real-world setting of clinical practice. *Is the four pillar approach feasible? Is it well tolerated?* And specifically, to the more recently introduced SGLT2i, *is their implementation and penetrance in routine clinical practice good? Are discontinuation rates like the one observed in clinical trials and in other observational studies?* The results of the BRING-UP 3 HF study seem to give positive answers to these important clinical questions which since now have not been widely addressed in the literature. To the best of our knowledge this is the first experience showing 6-months follow-up persistence data of this novel therapeutic approach strategy. In our study at 6 months the prescription rates of the four pillars remained stable or slightly increased with nearly two out of three patients treated with quadruple therapy. In the CONNECT-HF trial, which evaluated the effect of a hospital and post-discharge quality improvement intervention in participants with HFrEF in the US, the prescriptions rates were lower compared with ours and slightly decreased at 12 months.[11] In addition, SGLT2i prescription rates, which were already high at the end of the enrolment/discharge visit, increased to 84%, a percentage significantly higher than the 59% seen in the last observation period of the SwedeHF registry (second semester of 2022).[12] The overall discontinuation rate of the quadruple therapy at 6 months was almost 12% in the whole study population and occurred more frequently among patients enrolled during hospitalization then in the ambulatory setting: 18.6% vs 9.4%. Looking at the individual components of the quadruple therapy, we observed low discontinuation rates at 6 months (with MRAs being the most frequently discontinued). These were significantly lower than those reported in the EVOLUTION-HF study,[13] which recently described the use of GDMT in Japan, Sweden and the United States in contemporary real-world settings using an administrative database, or in the CHAMP-HF registry, which assessed discontinuation in the United States in the recent 'triple therapy era'.[9] We found a discontinuation rate of <5% for SGLT2i (again higher in the subset of hospitalized patients) which is one fourth than the one observed in the EVOLUTION-HF Study.[13] Interestingly, ARNIs, which are generally considered less easy to be managed in clinical practice, also raised to a prescription rate of 74%, were mostly prescribed over ACE-I/ARBs (15% at 6 months) and had even lower discontinuation rates compared with SGLT2i and about one fifth of the discontinuation rate observed in the EVOLUTION-HF Study.[13] The relatively high use of ARNIs compared with previous registries reflects widespread adoption due to more up-to-date data collection and the inclusion of centres with a specific expertise in heart failure management. Therefore it is possible to speculate that Italian cardiologists more often followed the American guideline approach (ARNIs preferred and ACE-I, to be used only in those patients who do not tolerate ARNIs)[5] than the ESC guideline approach (ACE-I/ARNI, with ARNIs as a substitute of ACE-I only in still symptomatic patients)[4] regarding the prescription of RASi. In addition, the 6-month diuretic prescription rate fell to 66%, at least in part due to the introduction of SGLT2i and ARNI treatment. Interestingly, in the ESC Heart Failure Long Term registry, 12-months prescription rates of diuretics remained high compared with baseline and close to 85%.[9] The prescription of vericiguat, recently reimbursed in Italy by the NHS at the time of data collection, showed a significant increase at 6 months follow-up. Reasons for non-prescription were mainly clinical and in line with those reported in other clinical registries (hypotension and bradyarrhythmia for BBs, hypotension and CKD or worsening renal function for RASi, CKD or worsening renal function and hyperkalaemia for MRAs). Interestingly, despite the high prevalence of hyperkalaemia as a reason for non-prescription, potassium binders were used in 2.4% and 3.0% at baseline and follow-up respectively. For SGLT2i previous or current genitourinary infections were the most common adverse reaction accounting for almost 30% of all investigator reported reasons, followed by CKD or worsening renal function. Similar explanations were found in the SwedeHF registry.[12] Some of these very well-known reasons and several other reported by investigators should not be considered real obstacles for treatment implementation with these life-saving treatments and scientific cardiovascular societies should act by promoting educational campaigns to further improve quality of care and appropriateness.

Target dose achievement at 6 months was overall poor particularly among patients enrolled during the acute phase. Suboptimal dose up-titration during follow-up is quite common and was found in the CONNECT-HF trial[11] as well in CHAMP-HF[14] and in the EVOLUTION-HF[13] registries with a longer follow-up visit than ours. The novel implementation strategy aiming to quickly have 'all on board' HF medications together with the difficulty in scheduling a tight follow-up schedule to reevaluate the effects of dose up-titration are probably the main reasons. The STRONG-HF trial confirmed that aggressive up-titration of GDMTs in the context of tight follow-up is feasible and positively impacts prognosis.[6] For most sites following HF patients this is quite complicated and there is a clear need of new strategies for GDMTs implementation and up-titration which have been shown to be effective[15,16] such as GDMT clinics, nurse-pharmacists led HF clinics and a wider use of telemedicine. Finally, the following were found to be independently associated to the prescription of quadruple therapy at 6 months: demographics (younger age) and enrolment setting related factors, non-ischaemic aethiology, absence of comorbidities (renal insufficiency and anaemia, but not iron deficiency) and of severity indicators (higher natriuretic peptides values and incident hospitalizations). Most of these factors were also reported by other authors in the CONNECT-HF Trial[11] and in other registries[12–14] and reinforce the principle that *one size does not fit all* in the management of patients with HF patients.

## Main limitations

Some limitations of our work must be acknowledged and should be addressed as follows: (i) patients were enrolled in a wide cardiology heart failure management oriented setting of care and therefore may not be

applicable to other cardiology or non-cardiology setting of care. (ii) This is a national registry, and high rates of quadruple therapy achieved may be also the result of Italian Health System which provides full coverage for GDMTs used in the management of HFrEF. (iii) The follow-up period is limited and results should be confirmed at 12 months to be fully comparable with other registries.

# Conclusions

In conclusion, we observed a high 6-month prescription rate of GDMTs in a contemporary real-world HFrEF population managed by cardiologists in Italy, including patients initially enrolled in the acute inpatient or outpatient setting. There is limited data in the literature on the 6-month persistence of the newly introduced four pillar strategy. Already at baseline, prescriptions were higher than in previous registries and remained high, showing that it is possible to narrow the gap between guideline recommendations for the implementation of GDMTs and clinical practice. Persistence with the four pillar combination is high and most discontinuations are for clinical reasons, some of which have been addressed and some of which need to be resolved. Dose uptitration is at least suboptimal and should be interpreted carefully as the result of a clinical decision (reduced perception of the need to really uptitrate) or organizational issues in the follow-up schedule.

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# Author contributions

Fabrizio Oliva (MD (Conceptualization; Funding acquisition; Investigation; Writing—original draft; Writing—review & editing)), Massimo Grimaldi (MD (Investigation; Writing—review & editing)), Maria Denitza Tinti (MD (Investigation; Writing—review & editing)), Giacomo Tini (MD (Investigation; Writing—review & editing)), Domitilla Russo (MD (Investigation; Writing—review & editing)), Alessandro Navazio (MD (Investigation; Writing—review & editing)), Maria Vittoria Matassini (MD (Investigation; Writing—review & editing)), Piero Gentile (MD (Investigation; Writing—review & editing)), Emilia D'Elia (MD (Investigation; Writing—review & editing)), Mariarosaria Catalano (MD (Investigation; Writing—review & editing)), Domenico Gabrielli (MD (Investigation; Writing—review & editing)), Stefano Carugo (MD (Investigation; Writing—review & editing)), Marco Marini (MD (Writing—review & editing)), Donata Lucci (Data curation; Formal analysis; Validation; Writing—review & editing), Massimo Iacoviello (MD (Investigation; Writing—review & editing)), Marco Gorini (Data curation; Validation; Writing—review & editing), Mauro Gori (MD (Writing—review & editing)), Andrea Di Lenarda (MD (Writing—review & editing)), Manlio Gianni Cipriani (MD (Investigation; Writing—review & editing)), Furio Colivicchi (MD (Investigation; Writing—review & editing)), Francesco Orso (MD (Conceptualization; Methodology; Visualization; Writing—original draft; Writing—review & editing)), Eleonora Bonvicini (MD (Investigation; Writing—review & editing)), and Aldo Pietro Maggioni (MD (Conceptualization; Funding acquisition; Validation; Visualization; Writing—original draft; Writing—review & editing)).

# Supplementary data

Supplementary data are available at *ESC Heart Failure* online.

# Declarations

## Disclosure of Interest

F.C., M.G.C., A.D.L., E.B., S.C., E.D., M.V.M., D.R., M.D.T., P.G., M.G. have no conflict of interest to disclose. F Oliva received personal fees from AstraZeneca, Novartis, Boehringer, Bayer, Menarini, Amgen, Sanofi, Novonordisk and participation in committees of studies sponsored by Novartis, Boehringer, Bayer, Sanofi, Amgen, AstraZeneca, Novonordisk not related to the current study. D.G. is the President of Heart Care Foundation and he participated in committee of Pure Study DSMB. M.G., D.L. and F.O. are employee of Heart Care Foundation, Florence, Italy. M.G. received personal fees from Boehringer, AstraZeneca, Novartis, Menarini, Amgen, Bayer and personal fees for participation in committees of studies sponsored by Amgen and Boehringer not related to the current study. M.I. received personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, Neopharmed Gentili, Bayer; support for attending meetings from AstraZeneca and received personal fees for consultancy in Advisory Board of studies sponsored by Eli Lilly, Boehringer Ingelheim, Novartis and Bayer not related to the current study. M.M. received honoraria for lectures and presentations from Astra Zeneca and Boehringer Ingelheim not related to the current study. A.N. received honoraria for lectures and presentations from Astra Zeneca, Novo Nordisk and Boehringer Ingelheim not related to the current study. M.C. received personal fees for scientist consultancy from Bayer. G.T. received speaker and travel fees from Alnylam, Takeda and Pfizer, not related to the current study. A.P.M. received personal fees for the participation in committees of studies sponsored by AstraZeneca, Bayer, Novartis, Sanofi not related to the current study.

## Data Availability

The data underlying this article will be shared on reasonable request to the BRING-UP 3 Heart Failure Steering Committee.

## Funding

The sponsor of the study was the Heart Care Foundation, a non-profit independent organization, which also owns the database. Database management, quality control of the data and data analyses were under the responsibility of the ANMCO Research Centre of the Heart Care Foundation. The study was funded by Heart Care Foundation with a partial unrestricted support from Boehringer-Ingelheim Italia, Eli-Lilly Italia, Novartis Farma SpA, Vifor Pharma Italia. Boehringer-Ingelheim Italia, Eli-Lilly Italia, Novartis Farma SpA, Vifor Pharma Italia had no role in the design, analysis or interpretation of the results in this study; Boehringer-Ingelheim Italia and Vifor Pharma Italia were given the opportunity to review the manuscript for medical and scientific accuracy, as well as intellectual property considerations. No compensation was provided to participating sites, investigators, or members of the Steering Committee. The Steering Committee of the study had full access to all of the data of this study and is taking complete responsibility for the integrity of the data and the accuracy of data analysis. The author(s) meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

## Ethical Approval

The study conforms with the principles outlined in the Declaration of Helsinki. The protocol has been approved by ethics committee in accordance with the national regulations. Each patient provided written informed consent to participate in the study.

## Pre-registered Clinical Trial Number

NCT06279988.

# Appendix

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