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ORIGINAL ARTICLE

Implementation of guideline-directed medical therapy in patients with heart failure with reduced ejection fraction (OpTIMa-HF Registry)

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Abstract

Aims The last released European guidelines on the management of heart failure (HF) recommend in patients with chronic HF with reduced ejection fraction (HFrEF) a pharmacological approach based on four fundamental drugs to be rapidly implemented and then uptitrated to modify disease progression. The aim of the Optimization of Therapy in the Italian Management of Heart Failure (OPTIMA-HF) registry is to collect data on chronic HF outpatients in different settings of care. In the present analysis, we report the first analysis of the OPTIMA-HF registry, focusing on the real-life use of guideline-directed medical therapy in patients affected by HFrEF.

Methods OPTIMA-HF is an observational, cross-sectional, multicentre, real-life Italian registry conducted in two different clinical settings: HF outpatients' clinics of Italian hospitals and community HF outpatients' services. The study comprises a

T0 phase—retrospective data collection, in which data of consecutive HF outpatients seen between January and October 2022 were collected; an educational activity phase; and a T1 phase—prospective data collection, in which data of consecutive HF outpatients seen between September 2023 and November 2023 were collected. In the present analysis, we describe the T0 phase focusing on HFrEF drug prescription rates, types, doses, combination therapy, the presence of contraindications and reasons of non-optimized treatment.

Results Twenty-nine centres enrolled 2110 HF patients, of which 1390 (65.9%) had HFrEF [69.5 ± 11.9 years, 76.2% males, 4.1 years since HF diagnosis, median ejection fraction (EF) 33%]. Among HFrEF patients, 89.1% were on treatment with renin–angiotensin–aldosterone system inhibitor (RAASi)/angiotensin receptor neprilysin inhibitor (ARNI) (72% ARNI and 17.1% RAASi), 95.1% with beta-blockers, 75.8% with mineralocorticoid receptor antagonists (MRA) and 63.2% with sodium/glucose cotransporter 2 inhibitors (SGLT2i). Despite high prescription rates, a non-negligible number of patients with no contraindications were not treated with each specific drug. Patients taking all four drug classes, as recommended by guidelines, were mere 46.9%. Regarding doses, a still low number of patients on RAASi/ARNI and beta-blockers were treated with a dose ≥50% of the target doses recommended by the European guidelines.

Conclusions The OPTIMA-HF registry reported that HFrEF fundamental drugs are prescribed in most Italian patients; however, <50% of patients receive optimal combination therapy, and still not a satisfying number of patients receive target doses. Strategies to improve implementation of guideline-directed medical therapy are needed to improve HF prognosis.

Keywords disease-modifying drugs; guideline-directed medical therapy; heart failure; HFrEF; pharmacotherapy

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Introduction

Heart failure (HF) is a clinical condition still burdened by high rates of morbidity and mortality, and the optimization of pharmacological treatment represents a crucial step to improve prognosis.[1] The 2021 European guidelines on the management of acute and chronic HF[2] recommend the rapid implementation of four disease-modifying drugs, including sodium/glucose cotransporter 2 inhibitors (SGLT2i) [irrespective of ejection fraction (EF)],[3] angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers and mineralocorticoid receptor antagonists (MRA) (all Class IA recommendation) for patients with HF with reduced EF (HFrEF). No specific sequence is advised on how to initiate these medications; instead, emphasis was given to modulation of the treatment schema according to the single patient's profile.[4] On the other hand, it was recommended to implement all four types of drugs in the shortest time possible without a compelling treatment sequence algorithm. Notably, this innovative recommendation of expedited implementation (ideally within 6 weeks) of all four classes of fundamental drugs, before dosage uptitration, implies a substantial change in clinical practice. The new therapeutic approach is grounded on the evidence of early clinical benefit that appears within a few weeks of administration for evidence-based medical treatment, is consistent across different combinations and dosages of background therapies, and is associated with an early reduction of major cardiovascular adverse events.[5] However, despite international recommendations and the strong evidence available, guideline-directed medical therapy (GDMT) prescription rates were low in recent registries,[6,7] for both new and 'historical' HF drugs that are often underprescribed despite no specific contraindication. For the Italian HF population, the last data reporting adherence to HF guidelines refer to the 2016 European Society of Cardiology (ESC) guidelines,[6] but no data are available following the 2021 guidelines recommendations.[2]

The aim of the Optimization of Therapy in the Italian Management of Heart Failure (OPTIMA-HF) registry was to collect data on HF patients followed in Italian outpatients' settings to describe the current national HF population with a specific focus on GDMT prescription and to assess the effects of educational activities on guidelines implementation. Specifically, in the present analysis, we focus on HFrEF treatment implementation and prescription rates, according to the current European guidelines.

Methods

Study design, procedures and population

OPTIMA-HF is an observational, cross-sectional, multicentre, real-life registry conducted in two different clinical settings: HF outpatients' clinics of Italian hospitals and community HF outpatients' services. The study comprises three phases:

(1) T0—retrospective data collection, in which participating centres were invited to collect data of consecutive HF outpatients seen between January 2022 and October 2022.

(2) Educational activity, in which three face-to-face educational meetings were conducted between October 2022 and December 2022 in the north, central and south Italian macroregions, followed by two online refresh meetings held between January and February 2023; these educational sessions included lectures from Italian opinion leaders in the field of HF, interactive clinical case presentations on different HF scenarios, revision of the study protocol and of the study database to clarify specific points, and collective discussion.
(3) T1—prospective data collection, in which participating centres were invited to collect data of consecutive HF outpatients seen from the fifth month up to the seventh month after the conclusion of the educational activity (September–November 2023), to avoid bias related to the educational meetings and to assess the impact of a quality improvement action on Italian cardiologists behaviours in the real-world HF setting.

To be included in the study, patients had to fulfil the following inclusion criteria:

(1) age ≥18 years;
(2) diagnosis of HF according to the ESC guidelines criteria[2];
(3) stable clinical conditions [New York Heart Association (NYHA) Classes I–III];
(4) outpatient setting; and
(5) capability to understand the study procedures and sign the informed consent form.

As exclusion criteria, we considered the standard criteria adopted in HF studies (*Table* S1) together with any clinical condition that would have jeopardized patient safety while participating in this study. For each patient, we collected demographic data and medical history; vital signs; cardiac rhythm and NYHA class reported at the time of the visit; HF type according to ESC criteria and HF aetiology assessed from clinical anamnesis and medical records; complete ongoing treatment and HF drug dose, including diuretics; presence of device and type; main available laboratory examinations related to HF, such as natriuretic peptides, renal function [estimated glomerular filtration rate (eGFR) was then calculated through the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula],[8] serum electrolytes, glycated haemoglobin and iron profile; and main available echocardiographic parameters, such as left ventricular diameters and volumes, EF, diastolic function, significant valvular disease, left atrial volume, right ventricular size and function, and systolic pulmonary artery pressure; when available, we also collected data on functional capacity, assessed through 6 min walking test and/or cardiopulmonary exercise test.

In the present analysis, we describe data regarding the T0 phase with a particular focus on HFrEF patients. In particular, we focused on HFrEF drug prescription, drug types and doses, rates of combination therapy, and presence and type of contraindication in patients not treated, considering for renin–angiotensin–aldosterone system inhibitor (RAASi)/ARNI [systolic blood pressure (SBP) <100 mmHg, eGFR < 30 mL/min/1.73 m^2 or potassium levels >5.2 mmol/L], for beta-blockers (SBP < 90 mmHg or heart rate <50 b.p.m.), for MRA (eGFR < 30 mL/min/1.73 m^2 or potassium levels >5.2 mmol/L) and for SGLT2i (eGFR < 20 mL/min/1.73 m^2 or SBP < 95 mmHg), as reported by the European guidelines.[2] As regards doses, according to treatment recommendations of the ESC guidelines,[2] we divided the reported doses into two groups: low dose (<50% of target dose) and intermediate–high dose (≥50% of target dose). Regarding combination therapy, we analysed all available combinations focusing on four-drug and three-drug combinations and performed a logistic regression analysis in patients taking three out of four drugs to describe the variables associated with non-prescription of the four pillars simultaneously.

HF with mildly reduced EF (HFmrEF) and HF with preserved EF (HFpEF) prescription patterns were not analysed in this report because the ESC update[3] on the pharmacological-specific treatment of these conditions is subsequent to the enrolment period of the T0 phase of the OPTIMA-HF registry and a focused data collection on these conditions is now ongoing.

The present research protocol complies with the World Medical Association Declaration of Helsinki, and it was approved by the Magna Græcia University of Catanzaro as the guiding study centre as well as by the local ethics committee of satellite centres. Each subject provided written informed consent to the study, including patients whose data were retrospectively collected and who could be reached by the investigators. The present study was registered at clinicaltrials.gov (NCT06287164).

Statistical analysis

Standard descriptive statistics were used to describe the sample: mean ± standard deviation or median with inter-quartile range (IQR) in case of numerical variables and absolute frequencies with percentages in case of categorical factors. Accordingly, the ANOVA, Kruskal–Wallis test or chi-squared test was used as an omnibus test to assess differences among groups. Due to the exploratory nature of the study, no correction for multiple comparison was adopted. Potential predictors of non-prescription of four-pillar combination therapy in patients taking three drugs were investigated using multivariable logistic regression models; results of the models were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical analyses were conducted using R Statistical Platform Version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

General characteristics of enrolled patients

In the T0 phase of the OPTIMA-HF registry, 29 centres participated in data collection, in particular 18 HF outpatients' clinics of Italian hospitals and 11 Italian community HF outpatients' services, homogeneously distributed across the national territory; participating hospitals were mainly tertiary referral centres. Overall, 2110 HF patients were enrolled in the registry (mean age 69.4 ± 12.3 years, 72.9% males) (*Table 1*), of whom 1390 (65.9%) were diagnosed with HFrEF (*Table 1*), 253 (12%) were affected by HFmrEF and 240 (11.4%) by HFpEF, 40 (1.9%) had a diagnosis of de novo HF and 187 (8.9%) had HF with improved EF (HFimpEF). Enrolled patients were in stable clinical conditions, with NYHA Classes I–III being present in more than 90% of subjects, median time from HF diagnosis was 4.1 years, cardiovascular risk factors and comorbidities distribution was in line as already reported in other registries, and in most patients (58.6%), HF was the consequence of ischaemic heart disease.

General characteristics and treatment prescription in HFrEF

HFrEF was the largest represented group among HF phenotypes (65.9% of enrolled patients). We focused the analysis on the treatment of this HF population, being the one with the largest options of medical treatments and the one with

Table 1 Baseline characteristics of patients enrolled in the Optimization of Therapy in the Italian Management of Heart Failure (OPTIMA-HF) registry.

	Overall (n = 2110)	HFrEF (n = 1390; 65.9%)
Age, mean ± SD	69.4 ± 12.3	69.5 ± 11.9
Male gender, *n* (%)	1538 (72.9)	1059 (76.2)
BMI, mean ± SD	26.8 ± 5.1	27.2 ± 4.7
Years of HF, median [IQR]	4.1 [0.8–5.3]	4.1 [0.7–5.1]
Aetiology		
Ischaemic, *n* (%)	1234 (58.6)	906 (65.3)
Idiopathic dilated cardiomyopathy, *n* (%)	459 (21.8)	300 (21.6)
Valvular heart disease, *n* (%)	131 (6.2)	56 (4)
Hypertensive heart disease, *n* (%)	87 (4.1)	31 (2.2)
Myocarditis, *n* (%)	18 (0.9)	9 (0.6)
Cardiotoxicity, *n* (%)	24 (1.1)	9 (0.6)
Other cardiomyopathies, *n* (%)	107 (5.1)	29 (2.2)
Other causes, *n* (%)	47 (2.2)	48 (3.5)
HHF in the last year, *n* (%)	512 (24.3)	381 (27.4)
EF, median [IQR]	36 [30–45]	33 [28–37]
TAPSE, mean ± SD	19.3 ± 3.7	18.8 ± 3.7
PAPs, mean ± SD	34.1 ± 10.3	35.0 ± 10.4
BNP, median [IQR]	414 [198–568]	435.5 [258–567.5]
NT-proBNP, median [IQR]	828 [441.8–1763.2]	878.5 [595.8–1827]
Potassium, mean ± SD	4.4 ± 0.5	4.3 ± 0.5
Hb, mean ± SD	13.3 ± 1.8	13.3 ± 1.8
eGFR, median [IQR]	63 [47–82]	62 [47–82]
SBP, mean ± SD	121.6 ± 17.5	119.1 ± 16.6
DBP, mean ± SD	73.6 ± 10.9	72.9 ± 10.8
HR, mean ± SD	69.8 ± 12.5	70.5 ± 12.5
Heart rhythm		
Sinus rhythm, *n* (%)	1137 (54)	738 (53.2)
Atrial fibrillation, *n* (%)	628 (29.8)	398 (28.7)
NYHA class		
I, *n* (%)	315 (15.1)	153 (11.1)
II, *n* (%)	1215 (58.4)	789 (57.4)
III, *n* (%)	519 (25)	409 (29.7)
IV, *n* (%)	31 (1.5)	24 (1.7)
Hypertension, *n* (%)	1604 (76.5)	1068 (77.1)
Diabetes, *n* (%)	732 (35.1)	510 (37.1)
Dyslipidaemia, *n* (%)	1477 (70.5)	1026 (74.1)
COPD, *n* (%)	447 (21.3)	327 (23.6)
CKD, *n* (%)	833 (44.1)	605 (47.5)

Abbreviations: BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2); COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; HR, heart rate; IQR, inter-quartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAPs, pulmonary artery systolic pressure; SBP, systolic blood pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

a well-defined recommended pharmacological approach at the time of patients' enrolment. HFrEF patients (n = 1390) had a mean age of 69.5 ± 11.9 years, 76.2% were males, median time from HF diagnosis was 4.1 years, median EF was 33% (IQR 28–37), mean N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were 878.5 pg/mL (IQR 595.8–1827), median eGFR was 62 mL/min/1.73 m^2 (IQR 47–82), and most patients were in NYHA Classes I–III, as reported in *Table* 1. As regards HF treatment (*Figure* 1), 89.1% of patients were treated with RAASi/ARNI, specifically 72% on ARNI and 17.1% on ACEi/angiotensin receptor blocker (ARB); 95.1% of patients were on treatment with beta-blockers (73.7% bisoprolol, 12.3% carvedilol, 10% metoprolol, 3.2% nebivolol and 0.8% other beta-blockers); MRA were prescribed in 75.8% of patients (47.8% spironolactone, 16.9% eplerenone and 35.3% treated with MRA not recommended by guidelines in HFrEF, specifically potassium canrenoate); and 63.2% of subjects were treated with SGLT2i (76% dapagliflozin, 23.6% empagliflozin and 0.4% treated with other SGLT2i, i.e., canagliflozin and ertugliflozin). Apart from the four recognized HFrEF-modifying drugs, 1052 patients were treated with loop diuretics (75.6%), of which 94.7% with furosemide at a mean dose of 55.5 mg/die and 5.3% with torasemide at a mean dose of 12.5 mg/die; 49.6% of patients had an implantable cardioverter-defibrillator (ICD), and 28.6% of patients had a cardiac resynchronization therapy (CRT).

Considering patients not on treatment with HF-recommended drugs, we observed that a non-negligible number of them had no contraindications to each specific drug (*Figure* 1, blue histograms). In particular, among patients not treated with ARNI, 24% had an SBP $>$ 100 mmHg, 23.4% had an eGFR $>$ 30 mL/min/1.73 m^2 and 21.7% had no hyperkalaemia; moreover, 16.1% of patients had none of the considered contraindications, thus were potentially eligible for ARNI prescription. As regards SGLT2i, 33.5% of non-treated patients had an SBP $>$ 95 mmHg, 34.7% had an eGFR $>$ 20 mL/min/1.73 m^2 and 31.8% had none of the considered contraindications, thus were potentially eligible for SGLT2i prescription (*Figure* 2).

Combination therapy and drug doses

Despite high prescription rates for each drug's class, the per cent of patients taking all four drug classes was 46.9% (40.6% on ARNI and 6.3% on ACEi/ARB combined with the other three recommended drug classes); in 34.3% of patients, three out of four drugs were used; in 14.4%, only two of four drugs were used; and 4.4% of patients were treated with one HF-recommended drug. Among patients taking three out of four drugs, the most used combination was ARNI/beta-blockers/MRA (14%). The prescription rates of four-drug combinations and of three-drug combinations including

Figure 1 Prescription rates of heart failure with reduced ejection fraction (HFrEF) drugs. Red bars refer to on-treatment patients; blue bars refer to non-treated patients without specific contraindications; and orange bars refer to non-treated patients with specific contraindications. For more details, please consult the main text. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium/glucose cotransporter 2 inhibitor.

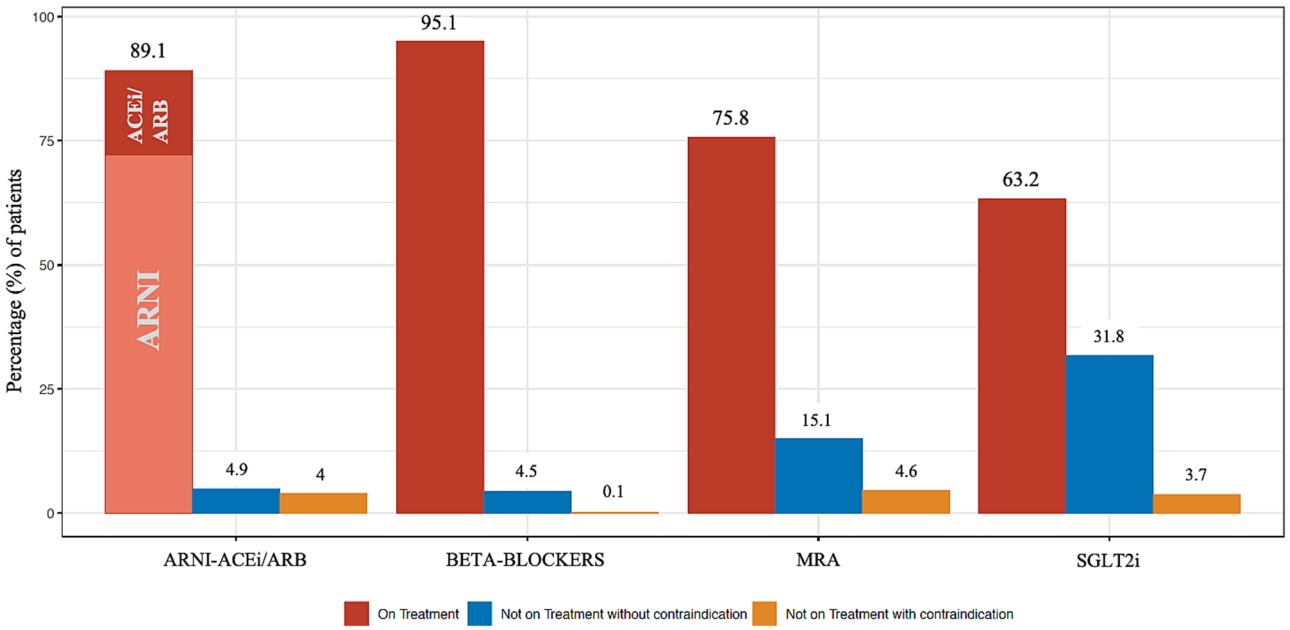

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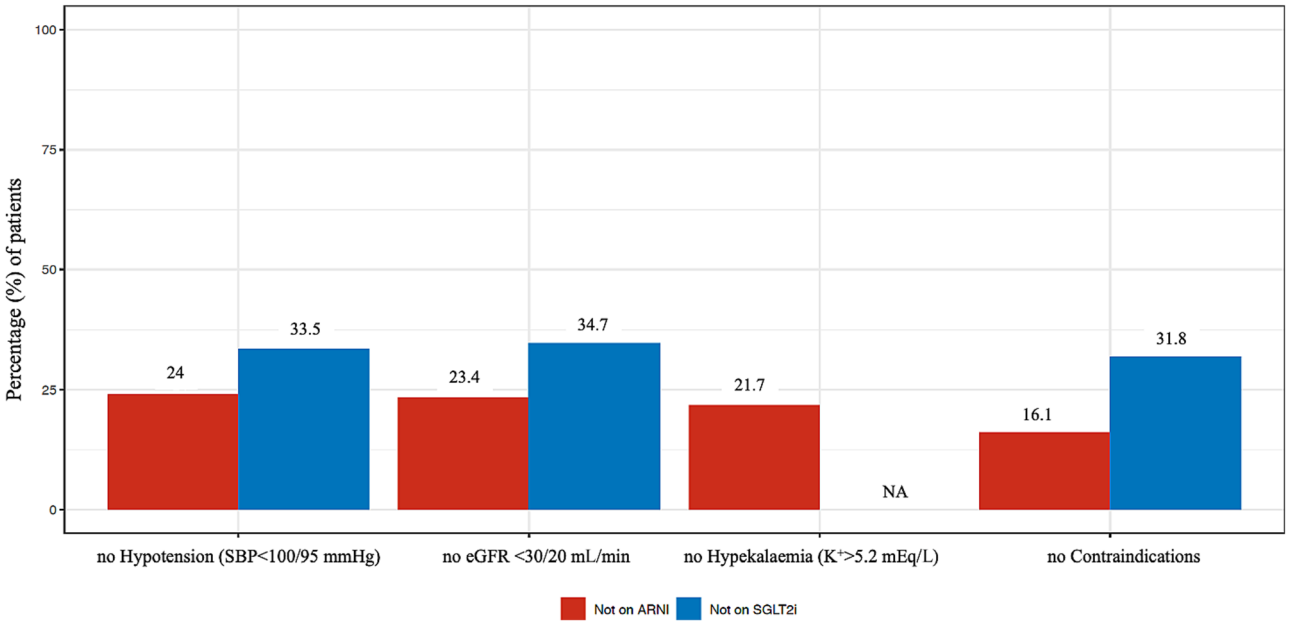
Figure 2 Rate of absence of main contraindications in patients not on treatment with angiotensin receptor neprilysin inhibitor (ARNI) or sodium/glucose cotransporter 2 inhibitor (SGLT2i). Red bars refer to the absence of reported specific condition in patients not on ARNI; blue bars refer to the absence of reported specific condition in patients not on SGLT2i. Hyperkalaemia is not reported for SGLT2i because this condition does not represent a contraindication for a SGLT2i prescription. For more details, please consult the main text. eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.



RAASi/ARNI + beta-blockers and MRA or SGLT2i are reported in *Figure* 3. Predictors of non-prescription of four-pillar combination therapy in patients taking three drugs were older age, male sex, non-ischaemic aetiology, higher EF and higher potassium levels (*Figure* S1).

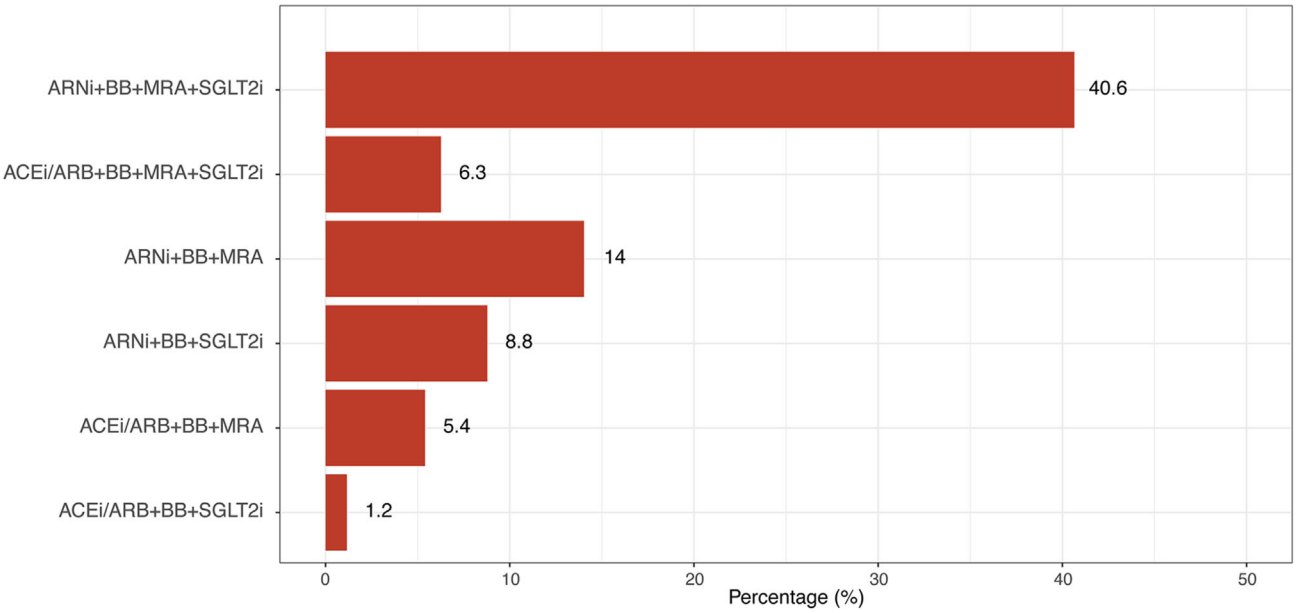
A not satisfying number of patients on RAASi/ARNI and beta-blockers were on treatment with a dose ≥50% of the target doses recommended by the European guidelines[2] (53.3% of patients on ARNI, 40.3% of patients on ACEi/ARB and 48.8% of patients on beta-blockers) (*Figure* 4). Conversely, 96.8% of patients on MRA reached an intermediate–high dose (*Figure* 4).

Considering both the drugs administered and their doses, we observed that only 1.1% of patients on treatment with all four fundamental drugs, considering the presence of ARNI, had all drugs at target dose, and no patients had all four drugs at target dose considering the presence of ACEi/ARB (*Figure* S2).

Discussion

The current study reports the first Italian analysis on the implementation of GDMT in patients affected by chronic HFrEF following the 2021 European guidelines on the management of acute and chronic HF.[2] The main finding of our registry is that each of four fundamental drugs recommended with Class IA in guidelines is prescribed in the majority of HFrEF patients followed in the Italian HF outpatients' setting. These four classes of drugs independently demonstrated a favourable prognostic effect in HFrEF with a reduction of HF hospitalization and mortality of 20% for ARNI compared with enalapril[9]; of ~30% for ACEis,[10,11] beta-blockers[12–16] and MRA[17,18] compared with placebo; and of ~25% for SGLT2i compared with placebo and in addition to recommended therapy.[19,20] Thus, the 2021 HF European guidelines[2] recommend that these drugs constitute the foundation of pharmacotherapy for patients with HFrEF and need to be integrated in the treatment within few weeks from patients' observation, ideally within hospital stay or shortly afterward.[3,21] Our findings show improved performance in HF drug prescription compared with a previous analysis of the Italian HF population reported in the phase 1 of the BLITZ-HF study[6] that reflected the 2016 European HF guidelines, where, at variance with the current guidelines, a stepwise approach to HFrEF therapy implementation was recommended. In particular, we observed slightly higher prescription rates of RAASi/ARNI (89.1% vs. 85.4%) with a remarkable increase in the prescription of ARNI (72% vs. 14.7%) reflecting the recent introduction of this drug class at the time of the BLITZ-HF study and a substantial change in practice thereafter. Moreover, we observed a comparable pre-

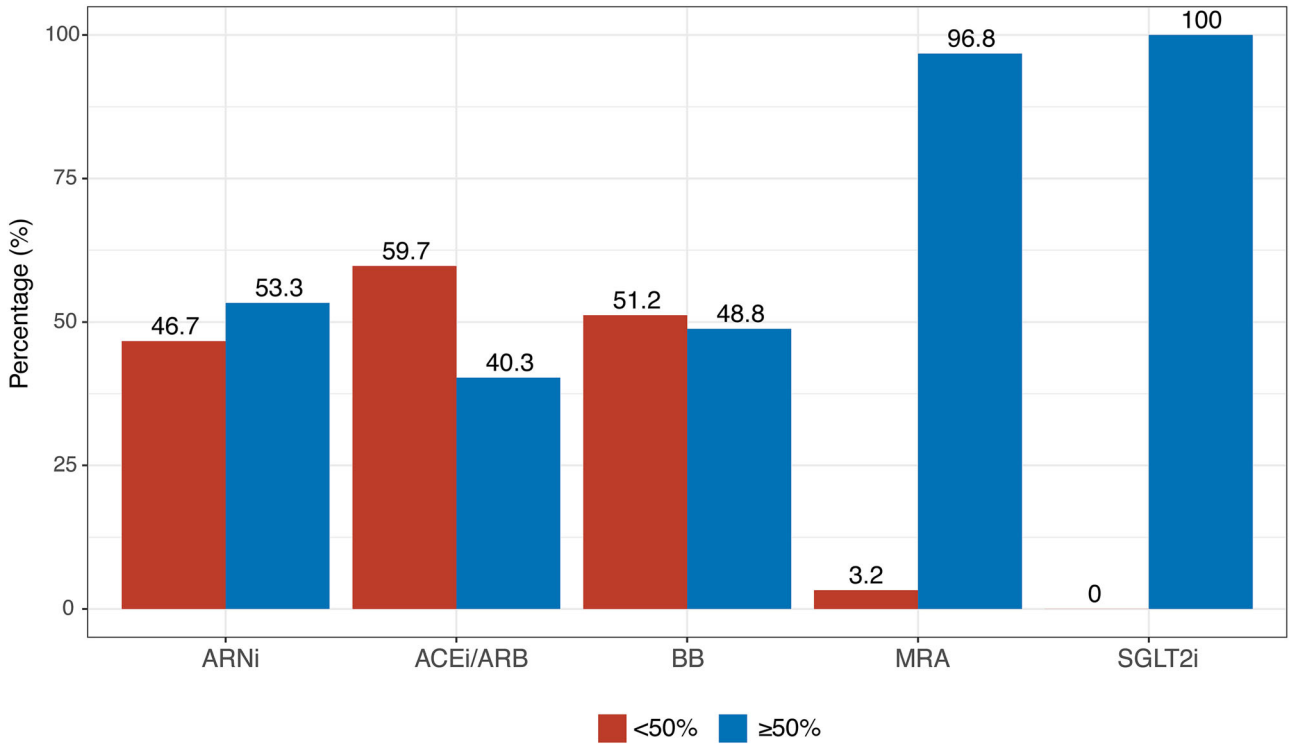
Figure 3 Prescription rates of heart failure with reduced ejection fraction (HFrEF) combination treatment. HFrEF patients taking all four drug classes were 46.9% [40.6% on angiotensin receptor neprilysin inhibitor (ARNI) and 6.3% on angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) combined with the other three recommended drug classes]; the remaining patients were treated with one, two or three out of four drugs. The four-drug combinations and the three-drug combinations including renin–angiotensin–aldosterone system inhibitor/ARNI + beta-blocker (BB) and mineralocorticoid receptor antagonist (MRA) or sodium/glucose cotransporter 2 inhibitor (SGLT2i) are reported in *Figure* 3. For more details, please consult the main text.



scription rate of MRA (75.8% vs. 72%) and of beta-blockers (95.1% vs. 94.2%). Notably, SGLT2i, for which the present analysis represents the first report of real-life use in our country since their introduction for HFrEF, were prescribed in 63.2% of patients, indicating rapid implementation in the clinical community. This likely reflects the high tolerability and efficacy of these drugs and the advantage of single dosage and once-daily administration.

The second relevant finding of the present analysis is the low rate of full combination therapy in HFrEF patients. International guidelines, both from Europe[2] and North America,[22] underline that the greatest prognostic benefit is reached when all four drug classes are simultaneously present, which is explained by the synergistic mode of action of these agents.[1] In fact, a calculated benefit of 1.4 years (for an 80-year-old) to 6.3 years (for a 55-year-old) of life prolongation with combined use of four classes was reported by Vaduganathan et al. based on computation of hazard ratios (HRs) for mortality observed in phase 3 clinical trials.[1] In our analysis, only 46.9% of patients were treated with all four drugs, including either combinations with ARNI or ACEi. Among patients taking three out of four drugs, the combination of ARNI, beta-blockers and MRA was the most common combination used (14%) and the combination of ACEi/ARB, MRA and SGLT2i was the least combination used (0.6%). SGLT2i was the class less used among patients taking three out of four drug classes. The BLITZ-HF study[6] reported a rate of RAASi/ARNI, beta-blockers and MRA combination, as recommended by the 2016 ESC guidelines, of 56.1%, which was 19.4% among patients receiving three out of four foundation drugs in our analysis. The lower reported rate of full combination therapy in our study, compared with the BLITZ-HF, reflects the recent adjunct of one additional class of drugs (SGLT2i) to the optimal therapy of HFrEF that in our country was available for HFrEF patients at the beginning of data collection for the current registry; remarkably, from January to October 2022, a steeply gliflozin prescription rate of 63% was reached in our HF outpatients, resulting in a full drug combination rate near to 50%. Compared with previous international registries, our data demonstrated better performance in HF drugs' prescription and in the use of combination therapy. In the CHAMP registry,[7] significant gaps in guideline-directed use of HF drugs were observed, with use of each recommended medication below 75% and a rate of combination therapy, based on RAASi/ARNI, beta-blockers and MRA, of 22.1%. In particular, 89.1% of our patients were treated with RAASi/ARNI (vs. 73.4% of the CHAMP registry), and ARNIs were administered to 72% of our patients compared with 12.8% of the CHAMP registry.[7] Differences in healthcare services between Italy and the United States might in part explain the dissimilar prescription rates of more consolidated HF drugs and the lower prescription rate of full combination therapy observed in the CHAMP analysis. Moreover, in Italy, all HF treatments are given from the national

Figure 4 Prescription rates of heart failure with reduced ejection fraction drug doses. According to the European Society of Cardiology guidelines recommendations, we divided the reported doses into two groups: low dose (<50% of target dose) and intermediate–high dose (≥50% of target dose). For more details, please consult the main text. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium/glucose cotransporter 2 inhibitor.



healthcare system free of charge to elderly and low-income patients and at a very low price to the others.

The additive beneficial impact of optimized combined therapy was recently underlined in a meta-analysis by Ameri et al.[23] assessing the efficacy of drugs developed after neurohormonal inhibition in patients with HFrEF, defined as the backbone of medical therapy for HFrEF, that is, ACEi/ARBs, MRA and beta-blockers. In patients with HFrEF, chronic kidney disease and clinical signs of poorly controlled HF despite optimized neurohormonal inhibition, the authors reported that SGLT2i, ARNI and ivabradine decreased the risk of cardiovascular death or HF hospitalizations by near 20% and vericiguat by around 10%, with the observation that SGLT2i and ARNI were most likely to improve prognosis, ivabradine was second most likely and vericiguat was third. Thus, combining the newest drugs with old drugs acting on neurohormonal inhibition provides incremental benefit in HFrEF, and improvement in the suboptimal optimization of therapy observed in our registry represents a clinical need for future strategies to reduce the high burden of mortality/morbidity in HFrEF patients. In the present report, according to the logistic regression analysis, the population in which we find some limitations in the clinical practice for treatment optimization is constituted by male patients with older age, non-ischaemic aetiology of HF, higher EF values and higher potassium levels. These data might help for the future identification of a target population in which the treatment needs to be implemented with specific and focused interventions.

Finally, despite high prescription rates of single HFrEF drugs, a still not satisfying number of patients on RAASi/ARNI were treated with an intermediate–high dose (≥50% of target dose), whereas 96.8% of patients on MRA reached an intermediate–high dose, however considering that for MRA, only two dosages (25 and 50 mg) are recommended by guidelines; thus, drug uptitration is more simple to afford; moreover, only 1.1% of patients on full combination treatment were at target dose for all HFrEF drugs. Although lower doses will usually be better tolerated in the short term, they might reduce long-term protection from disease progression, and patients with HF who are unable to tolerate target doses of disease-modifying therapies show worse prognosis.[24] Paolillo et al.[25] reported in 2017 an analysis on the association between beta-blocker dose and prognosis in a cohort of 5242 HFrEF patients derived from the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score database. Over a follow-up period of 3.58 years, a lower occurrence of a composite outcome of cardiovascular death, urgent heart transplantation or left ventricular assist device implantation was observed in high-dose (>25 mg carvedilol equivalent daily dose) patients than in medium-dose and

low-dose groups (12.5–25 and <12.5 mg carvedilol equivalent daily dose) (HR 1.97, $P < 0.001$; HR 1.95, $P = 0.001$, respectively). Yet Mohebi et al.[26] in 2022 reported that any dose of sacubitril/valsartan provides similar haemodynamic effects, and, in the PARADIGM-HF trial, a significant benefit of ARNI versus enalapril was observed at low dose, with no significant interaction compared with full dose, although patients receiving lower than target dose were at higher risk.[9]

Study limitations

The present study has few limitations, which must be acknowledged. First is the retrospective feature of the T0 phase: Even if consecutive retrospective enrolment was recommended, no ad hoc confirmation was performed to verify it. Moreover, the study started collecting data on all HF phenotypes, but in the present report, we focused only on HFrEF, because the 2023 ESC update[3] on the pharmacological treatment of HFmrEF and HFpEF was published after the conclusion of the T0 phase; thus, prescription patterns of these patients were not analysed in this report, and a focused data collection is now ongoing. In addition, although study sites were chosen to include a diverse composition of HF Italian outpatient services, the data reflect patients from sites who accepted to participate in the registry. Moreover, the participating hospitals were predominantly tertiary referral centres, and it is possible that the implementation of HFrEF medical treatment in these centres is different than the one adopted in lower referral sites. Thus, the reported results may not be generalizable to all care practices. No insights on the sequence and timing of drugs' prescription could be derived from our data, and, finally, the observational and retrospective nature of the study is unable to conclusively discern the underlying reasons of drug non-prescription.

Conclusions

The OPTIMA-HF registry, reporting the first real-life Italian HF population after the publication of 2021 ESC HF guidelines and after the introduction of SGLT2i in clinical practice, documents that single HFrEF drugs are very well prescribed; however, <50% of contemporary patients receive optimal drug therapy that includes the four foundation drugs recommended by the current ESC guidelines, and up to one third of patients not receiving ARNI or SGLT2i are potentially eligible to do so. Besides, a not satisfying number of patients receive target doses. Strategies to improve implementation of GDMT in clinical practice are needed to improve prognosis in HF patients.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

Supporting information

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

Figure S1. Predictors of non-prescription of the 4-pillars combination. Odds ratios (ORs) and 95% confidence intervals from the multivariable logistic regression performed on the reported variables to assess those related with non-optimized treatment with all 4-pillars combination therapy in patients on 3 drugs. eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; HR, heart rate; CRT, Cardiac Resynchronization Therapy; ICD, Implantable Cardioverter-Defibrillator; BMI, Body mass index.

Figure S2. Prescription rates of target doses in patients on combination therapy. Left-side bars show the percentage of patients on combination treatment with ACEi/ARB, beta-blockers, MRA, and SGLT2i and at target dose for each single drug and for all four pillars (green bar, 0% in this specific case). Right-side bars show the percentage of patients on combination treatment with ARNI, beta-blockers, MRA, and SGLT2i and at target dose for each single drug and for all four pillars (green bar, 1.1% in this specific case). ARNI, Angiotensin Receptor Neprilysin Inhibitor; ACEi, Angiotensin-Converting Enzyme inhibitors; ARB, angiotensin-receptor blockers; BB, beta-blockers; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium/glucose cotransporter 2 inhibitors.

Table S1. Exclusion Criteria for the participation in the Optimization of Therapy in the Italian Management of Heart Failure [OpTIMa-HF] Registry.

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