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Original Article

Educational professional activities for enhancing heart failure guidelines implementation: data from the Optimization of Therapy in the Italian Management of Heart Failure (OpTIMa-HF) Registry

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ABSTRACT

Background: European guidelines recommend for heart failure with reduced ejection fraction (HFrEF) rapid initiation and later up-titration of four foundation drugs. We assessed whether an educational intervention might improve guideline-directed medical therapy (GDMT) use in Italian clinical practice.
Methods: OpTIMa-HF is a multicenter observational registry including 29 Italian centers (hospital- and community-based HF outpatient clinics). The protocol included a retrospective phase (T0; January–October 2022), an educational intervention, and a prospective enrolment (T1; September–November 2023). HFrEF patients in retrospective and prospective phases were compared. Outcomes were prescription rates of GDMT drugs, combination therapy, management of contraindications, and drugs doses, adjusted for multiple comparisons using the Holm-Bonferroni procedure.
Results: A total of 1,390 HFrEF patients were analyzed in T0 and 1,292 in T1. Patients enrolled in T1 were slightly older (70.5 vs 69.5 years; p=0.032), with similar sex distribution. After multiple comparisons, prescription rates increased for mineralocorticoid receptor antagonists (MRA, 75.8% vs 81.4%, p=0.040) and sodium–glucose co-transporter-2 inhibitors (SGLT2i, 63.2% to 80.3%, p<0.001), compared to T0. Quadruple therapy increased by approximately 30% (46.9% vs 61% p<0.001) and was stable after multiple comparisons, as the proportion of

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patients not receiving SGLT2i despite no contraindications that decreased from T0 to T1 (31.8% vs 17.1%; p<0.001).

Conclusions: In patients with HFrEF educational activities are associated with improvement in guidelines recommended drugs implementation and might represent a feasible strategy to improve clinical practice.

1. Introduction

Heart failure (HF) remains a clinical condition characterized by elevated mortality and hospitalization rates. Treatment optimization, according to international guidelines recommendations, is of crucial importance to improve long-term prognosis, but guidelines implementation remains suboptimal. Thus, educational and learning activities directed to healthcare professionals involved in the management of patients at risk or affected by HF maybe warranted to disseminate and implement use of guidelines in clinical practice. A previous Italian experience from the BLITZ-HF study (1), referred to the 2016 European HF guidelines (2), showed that a structured educational intervention was helpful in improving healthcare professionals' performance and disease management. In 2025 a report from the Optimization of Therapy in the Italian Management of Heart Failure (OpTIMa-HF) registry (3), focused on patients with HF with reduced ejection fraction (HFrEF), showed, in the first real-life Italian data collection after the publication of 2021 ESC HF guidelines (4), elevated prescription rates of single foundational HFrEF drugs, but with less than 50% of patients receiving optimal combination therapy including the four foundation drug classes (Angiotensin receptor-neprilysin inhibitors – ARNI, beta-blockers, mineralocorticoid receptor antagonists – MRA, and Sodium/glucose cotransporter 2 inhibitors - SGLT2i) recommended by the ESC guidelines. In addition, less than 50% of patients received target doses of drugs. After completing data collection of the first OpTIMa-HF Registry report, structured educational interventions focused on HF management according to the current ESC guidelines were conducted, involving all enrolling centers. Aim of the present analysis is to describe the role of these learning activities in the improvement of HF centers performance for the management of HFrEF in the Italian clinical practice.

2. Methods

2.1. Study Design

The study design has been previously described (3). Briefly, OpTIMa-HF (NCT06287164) is an observational, cross-sectional, multicenter, real-life registry conducted across Italian hospital-based HF outpatient clinics and community-based HF outpatient services. The present study has a bidirectional design, integrating both retrospective and prospective data collection. Specifically, it was composed by three different phases: a retrospective data collection (T0, from January to October 2022), an educational activity phase, and a prospective data collection on HF outpatients (T1). The results of the retrospective data collection have been previously reported (3). The educational activity consisted of three face-to-face educational 2-days meetings held across northern, central, and southern Italy between October and December 2022, followed by two online sessions in early 2023. The first in person event started with an expert lecture on current HF Guidelines, followed by interactive clinical cases discussions on the reported topics, detailed revision of the study protocol and database, discussion on retrospective phase results and collective debate. The second and third face-to-face meetings focused on major clinical trials on new HF drugs and on HF integrate management, including data presentation and consequent debate on therapeutic inertia, and adherence and persistence to HF treatment over time, followed by interactive clinical cases discussions on the reported topics. The two online meetings were Q&A based sessions with experts in the field in order to clarify any doubt or unsolved issue.

To minimize potential bias related to the proximity of the educational meetings, the T1 prospective data collection phase was conducted between September and November 2023, that is several months after the educational activity, allowing for a more accurate assessment of its impact on the clinical practice.

Full methodological details, including patient inclusion/exclusion criteria and data collection procedures, have been previously reported (3). In the previous report we described the population enrolled during T0 phase, with a specific focus on HFrEF patients. In the present analysis, we focus on patients with HFrEF enrolled during the T1 phase and compare these data with those collected retrospectively during the T0 phase, in order to evaluate the impact of the educational intervention on Italian cardiologists' behaviors in the real-world HF setting.

Specifically, we analyzed prescription rates, drug classes and dosages, patterns of combination therapy, and reasons for non-prescription of new HF drugs based on guideline-defined contraindications in patients with HFrEF. Contraindications were defined as follows: for ARNI systolic blood pressure (SBP) <100 mmHg, eGFR <30 ml/min/1.73m^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 European Guidelines (4). Drug doses were categorized as low (<50% of target dose) or intermediate-high (≥50%), as per guideline recommendations (4). We also examined the use of combination therapy, focusing on the recommended HFrEF 4-drugs regimen.

To confirm study results and overcome baseline difference between the retrospective and prospective cohort we performed an adjunctive analysis on HF treatment implementation considering the subgroup of patients with available data at both assessments (T0 and T1). In this subgroup we analyzed differences in HFrEF drugs' prescription rates and patterns of combination therapy, also evaluating the balance between treatment initiation and discontinuation at the analyzed timepoints.

2.2. Ethical conduct of the study

The study was approved by the Magna Graecia University of Catanzaro and reviewed by an independent ethics committee in each center. The study was performed according to the World Medical Association Declaration of Helsinki. Each subject provided written informed consent to the study. The present study was registered in clinicaltrials.gov (NCT06287164).

2.3. Statistical Analysis

Standard descriptive statistics were used to describe the sample: mean ± standard deviation or median with interquartile range in case of numerical variables and absolute frequencies with percentages in case of categorical factors. Accordingly, T test for independent samples, Mann-Whitney U test or the chi-square test were used as omnibus test to assess differences among groups. For patients with available data at both assessments, changes in drug utilization between the two time points were evaluated using the McNemar test. For families of related comparisons, p-values were adjusted for multiple comparisons using the Holm-Bonferroni procedure. Results were considered statistically significant if p-value was less than 0.05. All statistical analyses were conducted using R Statistical Platform version 4.2.2 (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. General characteristics of enrolled patients with HFrEF

A total of 29 centers (18 hospital-based HF outpatient clinics and 11 community-based HF outpatient services), homogeneously distributed across Italy, were involved in both the retrospective (T0) and prospective (T1) phases of the OpTIMa-HF Registry. All centers participated at 70% or more of proposed educational activities.

Overall, 2110 HF patients were enrolled in the T0 phase, of which 1390 (65.9%) were diagnosed with HFrEF, and 2110 HF patients were enrolled in the T1 phase, of which 1292 (61.6%) with HFrEF. We focused the present analysis on patients with HFrEF, being the largest represented group among HF phenotypes and having the most clearly defined therapeutic approach according to current guidelines (4). Baseline characteristics of HFrEF patients enrolled during the T1 phase, and their comparison with those enrolled in the T0 phase, are reported in Table 1.

HFrEF patients (n=1292) enrolled in T1 phase had a mean age of 70.5±11.4 years, 77% were males, median time from HF diagnosis was 2.9 years, median EF was 34% (IQR 30-38), median NT-proBNP levels were 783 pg/mL (IQR 376-1900), and median eGFR was 63.2 ml/min/1.73 m^2 (IQR 45.6-82.2). Patients were in stable clinical conditions, with the majority in NYHA class I-III (98.5%). Compared to patients with HFrEF enrolled in the T0 phase, patients at T1 were slightly older (70.5 ± 11.4 vs. 69.5 ± 11.9 years; p = 0.032) but did not differ in sex distribution. Ischemic etiology was more common at T0 (65.3% vs. 58.4%; p < 0.001). Median EF was slightly different between T0 and T1, despite not clinically relevant (34% vs. 33%; p < 0.001), while sinus rhythm was more frequent at T1 (58.7% vs. 53.2%). As regards comorbidities, chronic kidney disease (CKD), defined as eGFR <60 ml/min/1.73 m^2, was less represented at T1 (42.3% vs. 47.5%; p = 0.010). No differences were observed in prevalence of diabetes, hypertension, chronic obstructive pulmonary disease (COPD) or HF hospitalization in the previous year.

Table 1
Comparison of Baseline Characteristics of HFrEF Patients Enrolled during T0 and T1 Phases.

	T0 (n=1390)	T1 (n=1292)	p value
Age, mean ± SD	69.5±11.9	70.5±11.4	0.032
Male gender, n (%)	1059 (76.2)	995 (77)	0.646
BMI, mean ± SD	27.2±4.7	27.4±5.2	0.443
Years of HF, median [IQR]	4.1 [0.7; 5.1]	2.9 [0.5; 8]	0.246
Etiology			<0.001
Ischemic, n (%)	906 (65.3)	754 (58.4)	
Idiopathic dilated cardiomyopathy, n (%)	300 (21.6)	213 (16.5)	
Valvular heart disease, n (%)	56 (4)	53 (4.1)	
Hypertensive heart disease, n (%)	31 (2.2)	79 (6.1)	
Myocarditis, n (%)	9 (0.6)	12 (0.9)	
Cardiotoxicity, n (%)	9 (0.6)	10 (0.8)	
Other cardiomyopathies, n (%)	29 (2.2)	108 (8.4)	
Other causes, n (%)	48 (3.5)	61 (4.7)	
HHF in the last year, n (%)	381 (27.4)	342 (26.5)	0.623
EF, median [IQR]	33 [28; 37]	34 [30; 38]	<0.001
BNP, median [IQR]	435.5 [258; 567.5]	563 [234; 821]	<0.001
NT-proBNP, median [IQR]	878.5 [595.8; 1827]	783 [376; 1900]	0.008
Hb, mean ± SD	13.3±1.8	13.5±1.8	0.008
eGFR, median [IQR]	61.7 [47; 81.5]	63.2 [45.6; 82.2]	0.696
SBP, mean ± SD	119.1±16.6	120±16.2	0.18
DBP, mean ± SD	72.9±10.8	72.2±10.5	0.121
HR, mean ± SD	70.5±12.5	67.9±12.8	<0.001
Heart Rythm			<0.001
Sinus rythm, n (%)	738 (53.2)	734 (58.7)	
Atrial fibrillation, n (%)	398 (28.7)	240 (19.2)	
NYHA Class			<0.001
I, n (%)	153 (11.1)	174 (13.6)	
II, n (%)	789 (57.4)	858 (67.1)	
III, n (%)	409 (29.7)	228 (17.8)	
IV, n (%)	24 (1.7)	19 (1.5)	
Hypertension, n (%)	1068 (77.1)	997 (77.4)	0.865
Diabetes, n (%)	510 (37.1)	470 (36.6)	0.837
Dyslipidemia, n (%)	1026 (74.1)	1014 (78.7)	0.006
COPD, n (%)	327 (23.6)	278 (21.6)	0.228
CKD, n (%)	605 (47.5)	544 (42.3)	0.010

SD, standard deviation; BMI, body mass index; IQR, interquartile range; HHF hospitalization for heart failure; EF ejection fraction; BNP brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease (defined as eGFR <60 ml/min).

3.2. Treatment prescription rates in HFrEF

In the prospective phase, 91.4% of patients were treated with RAASi/ARNI, specifically 75.8% was on ARNI and 15.6% on ACEi/ARB, 95.6% of patients were on treatment with beta-blockers (77.3% bisoprolol, 9.6% carvedilol, 9.9% metoprolol, 2.1% nebivolol, and 1.1% other beta-blockers), MRAs were prescribed in 81.4% of patients (26.7% spironolactone, 19.7% eplerenone, and 53.6% potassium canrenoate), and 80.3% of subjects were treated with SGLT2i (66.0% dapagliflozin, 33.9% empagliflozin, and 0.1% treated with canagliflozin). Besides, 900 patients were treated with loop diuretics (70.1%), of which 97.8% with furosemide at a mean dose of 52 mg/die and 2.2% with torasemide at a mean dose of 13.5 mg/die; 41.5% of patients had an Implantable Cardioverter-Defibrillator (ICD) and 26.9% of patients a Cardiac Resynchronization Therapy (CRT).

Compared to T0 phase, a variation in prescription rates of ARNI (72.2% vs. 75.8%; p=0.035), MRA (75.8% vs. 81.4%; p=0.01) and SGLT2i (63.2% vs. 80.3%; p < 0.001) was observed at T1. However, following correction for multiple comparisons, the increase in ARNI prescription lost statistical significance (adjusted p=0.105), whereas a stable increase was confirmed for MRA (p=0.04) and SGLT2i (p<0.001) (Fig. 1).

Among patients not on treatment with ARNI and SGLT2i during T0 phase, a sizable proportion of them had no contraindications to each specific drug. In particular, among patients not treated with ARNI, 16.1% had no contraindications (SBP <100 mmHg, eGFR <30 ml/min/1.73 m^2, or no hyperkalemia), being potentially eligible to ARNI treatment. This proportion showed a slight reduction at T1, declining to 14.6% (p = 0.285) (Fig. 2). For SGLT2i, 31.8% of non-treated patients at T0 had no contraindications (SBP <95 mmHg or eGFR <20 ml/min/1.73 m^2), indicating potential eligibility. This percentage decreased to 17.1% at T1 (p < 0.001), and remained stable after correction, probably suggesting improved alignment with GDMT after the educational activity (Fig. 2).

3.3. Combination therapy and drugs doses

Despite high prescription rates for each drug's class, during the T0 phase, the percentage of patients taking all four foundation drugs was 46.9% (40.6% on ARNI and 6.3% on ACEi/ARB combined with the other 3 recommended drug classes); at T1 this proportion increased to 61% (p<0.001), corresponding to a 30% increase. This variation remained stable after adjustment for multiple comparisons. In particular, the percentage of patients treated with ARNI alongside with the other three recommended drug classes increased from 40.6% in the T0 to 53.4% (p<0.001). Differences in prescription rates of 4-drugs combinations between T0 and T1 are reported in Fig. 3.

At T0, a suboptimal proportion of patients receiving RAASi/ARNI and beta-blockers were treated with doses ≥50% of the target doses recommended by the European Guidelines (4), with only 53.3% of patients on ARNI, 40.3% on ACEi/ARB, and 48.8% on beta-blockers

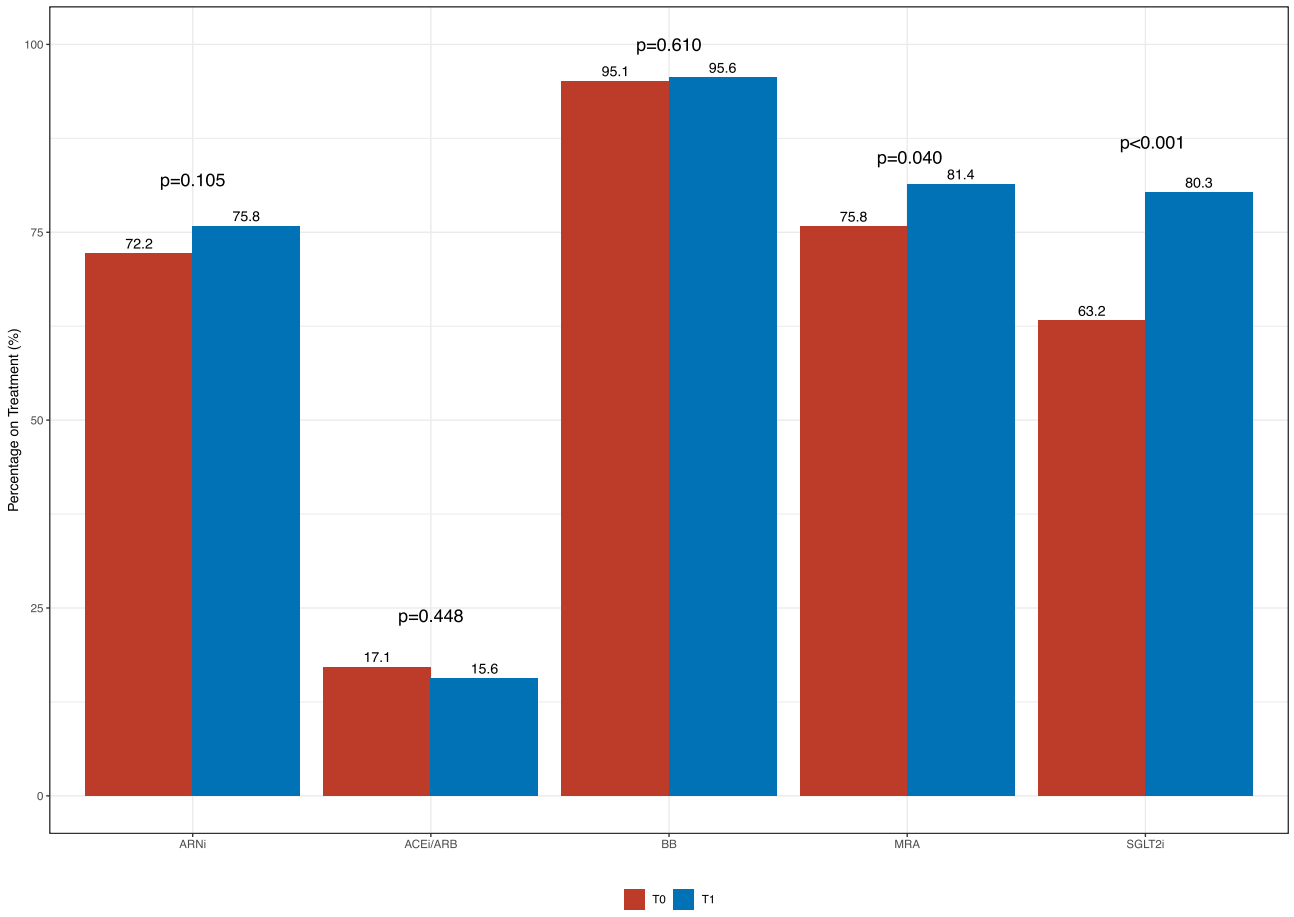


Fig. 1. Changes in prescription rates of HFrEF therapies between T0 and T1. Bar graph showing the percentage of patients receiving HFrEF drugs (ARNI, ACEi, ARB, MRA, SGLT2i), at T0 (red) and T1 (blue), respectively. P-values were adjusted for multiple comparisons using the Holm-Bonferroni method. *ARNI, Angiotensin Receptor Neprilysin Inhibitor; ACEi, Angiotensin-Converting Enzyme inhibitors; ARB, angiotensin-receptor blockers; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium/glucose cotransporter 2 inhibitors.*

reaching this threshold, and 96.8% of patients on MRA received an intermediate-high dose (Fig. 4). At T1, these proportions showed a slight but not significant increase either before or after adjustment for multiple comparisons: 53.4% for ARNI, 43.0% for ACEi/ARB, and 52.4% for beta-blockers, while the percentage of patients on MRA at an intermediate-to-high dose remained high (95.8%) (Fig. 4).

3.4. GDMT implementation in patients with both assessments (T0 and T1)

When analyzing the subgroup of patients (n=437) who underwent both T0 and T1 assessments a significant increase in prescription rates from T0 to T1was observed for ARNI (+4.4%, p=0.005), MRA (+3.9%, p=0.008), and SGLT2i (+13%, p<0.001), consistent with the whole group analysis. These changes reflected a favorable balance between treatment initiation and discontinuation, with 6.5% vs 2.9% for ARNI, 5.9% vs 2.0% for MRA, and 15.6% vs 2.6% for SGLT2i, respectively. Following correction for multiple comparisons, the p-values increased for prescription rate of ARNI (adjusted p=0.02) and MRA (adjusted p=0.02), with no changes for SGLT2i (adjusted $p < 0.001$) (Supplementary Fig. 1A). Similarly, a significant increase in the percentage of patients receiving ARNI-based quadruple therapy was observed at T1 (+10%, p<0.001), whereas no significant differences were observed for ACEi/ARB-based quadruple therapy (Supplementary Fig. 1B), either before or after adjustment for multiple comparisons.

4. Discussion

The results of the present analysis show that in the setting of HF therapeutic management, a structured educational intervention might contribute to improve physicians' performance according to international guidelines recommendations. In particular, we observed an improvement in three main components of HFrEF treatment. First, a substantial increase in the prescription rate of HFrEF foundational drugs, as MRA (75.8% vs. 81.4%) and SGLT2i (from 63.2 to 80.3%), was observed, that remained stable after adjustment for multiple comparisons, reflecting an increased awareness of the prognostic relevance of these drugs in HFrEF treatment; ARNI prescription rate was slightly different at baseline analysis, however remained no longer significant after correction. Second, a decrease in the number of patients with no contraindication, that were not treated with SGLT2i, from 31.8% at T0 to 17.1% at T1 ($p < 0.001$) was detected, reflecting an improved alignment with GDMT; a similar but not significant trend was also observed for ARNI, whose rate of non-prescription in potentially eligible patients declined form 16.1% a T0 to 14.6% at T1 ($p = 0.285$). Third, and most important, an increase in the proportion of HFrEF patients receiving a 4-drugs combination regimen that varied from a rate below 50% at T0 (i.e. 46.9%) to 61% at T1 ($p < 0.001$) was reported, stable after adjustment for multiple comparisons, with an improvement of the subgroup of patients receiving an ARNI-based combination strategy (from 40.6% to 53.4%, $p < 0.001$). Conversely, no substantial changes were observed in the proportion of patients receiving ≥50% of the target doses recommended by the European Guidelines. However, the design of

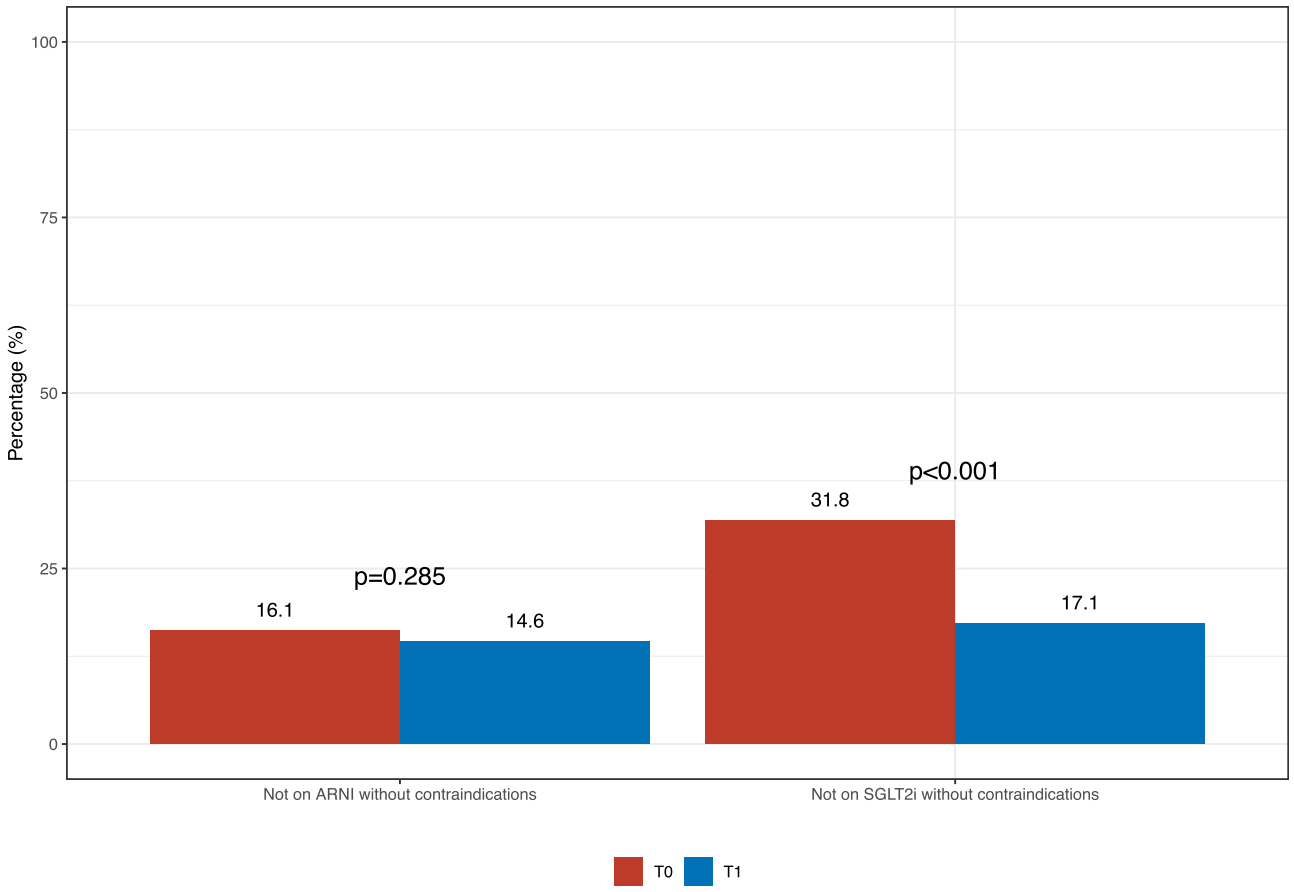


Fig. 2. Changes in the percentage of patients not on treatment with ARNI or SGLT2i without contraindications between T0 and T1. Bar graph showing differences in the percentage of patients not on treatment with ARNI or SGLT2i in absence of main contraindications, at T0 (red) and T1 (blue), respectively. P-values were adjusted for multiple comparisons using the Holm-Bonferroni method. *ARNI, Angiotensin Receptor Neprilysin Inhibitor; SGLT2i, sodium/glucose cotransporter 2 inhibitors.*

the study and the absence of a contemporaneous control group, limits a causal ascription of the observed results solely to the reported educational intervention.

In the setting of HFrEF, it is well known that an optimized pharmacological therapy is crucial to improve long-term prognosis. Specifically, the 2021 European guidelines on the management of HF (4) recommend the fast implementation of four disease-modifying drugs, including ACEi/ARNI, beta-blockers, MRA, and SGLT2i (all Class IA recommendation) in the shortest time possible, for the treatment of HFrEF. In our patients' population, the prescription of single HFrEF drugs was quite high at baseline (3) and increased after the educational interventions, in particular for MRA and SGLT2i. Yet, our patients were already diagnosed with HFrEF, and, therefore, the time elapsing from first diagnosis to optimization of therapy and the sequence of drugs prescription remains to be addressed in observational studies in the de novo HFrEF population.

However, apart from the prescription of single drugs, the main component of HFrEF treatment is the combination of all these foundational drugs, without a specific sequence schema, but with a modulation of the treatment algorithm according to the single patient's profile. Several analyses have demonstrated the prognostic importance of such treatment combinations in the clinical practice. Specifically, Vaduganathan et al. (5) showed that an optimized pharmacological therapy with complete disease modifying drugs is responsible for a further decrease in the risk of cardiovascular death or hospital admission for HF (more than 60%) when compared with limited conventional therapy (one or two HF drugs). Moreover, they reported a consistent lifetime benefit derived from an optimized and combined treatment, suggesting a potential event-free survival gain of up to 8 years with a longer projected survival for younger patients. Similarly, a recent metanalysis including 103,754 patients across 89 randomized controlled trials of HFrEF treatment (6), demonstrated that quintuple therapy with ARNI, beta-blockers, MRA, SGLT2i, and vericiguat was most effectively in reducing all-cause mortality compared to placebo (HR: 0.35; 95% CI: 0.27-0.45), followed by quadruple therapy with ARNI, beta-blockers, MRA, and SGLT2i (HR: 0.39; 95% CI: 0.32-0.49), also confirming that for a typical 70-year-old HFrEF patient, quadruple therapy provided a lifetime benefit of additional 5.3 years (95% CI: 2.8-7.7) compared to no treatment. Thus, adherence to guidelines recommendations is crucial in clinical practice to improve patients' outcome and physicians' adherence to guidelines has been associated with improved outcomes in ambulatory patients affected by HFrEF (7). In this context, structured educational activities, directed both to patients and to physicians, are recognized as valuable tools to improve the application of guidelines in the clinical practice (8). In our analysis, educational activity seemed to be useful in improving physicians' performance in the setting of combination therapy, showing a rate of 4-drugs therapy raising from 46.9% to 61% ($p<0.001$) and a trend for dose increase of ACEi/ARB and beta blockers.

Yet, in the real-life, several factors still limit the application of guidelines, including conditions related to physicians, as therapeutic inertia, lack of awareness, lack of time, different healthcare resources, and complexity of treatment prescription modalities; conditions related to patients, as age, sex disparities, presence of comorbidities, side-effects, and contraindications, and conditions related to guidelines, as length of documents, complexity of recommendations, and inadequate

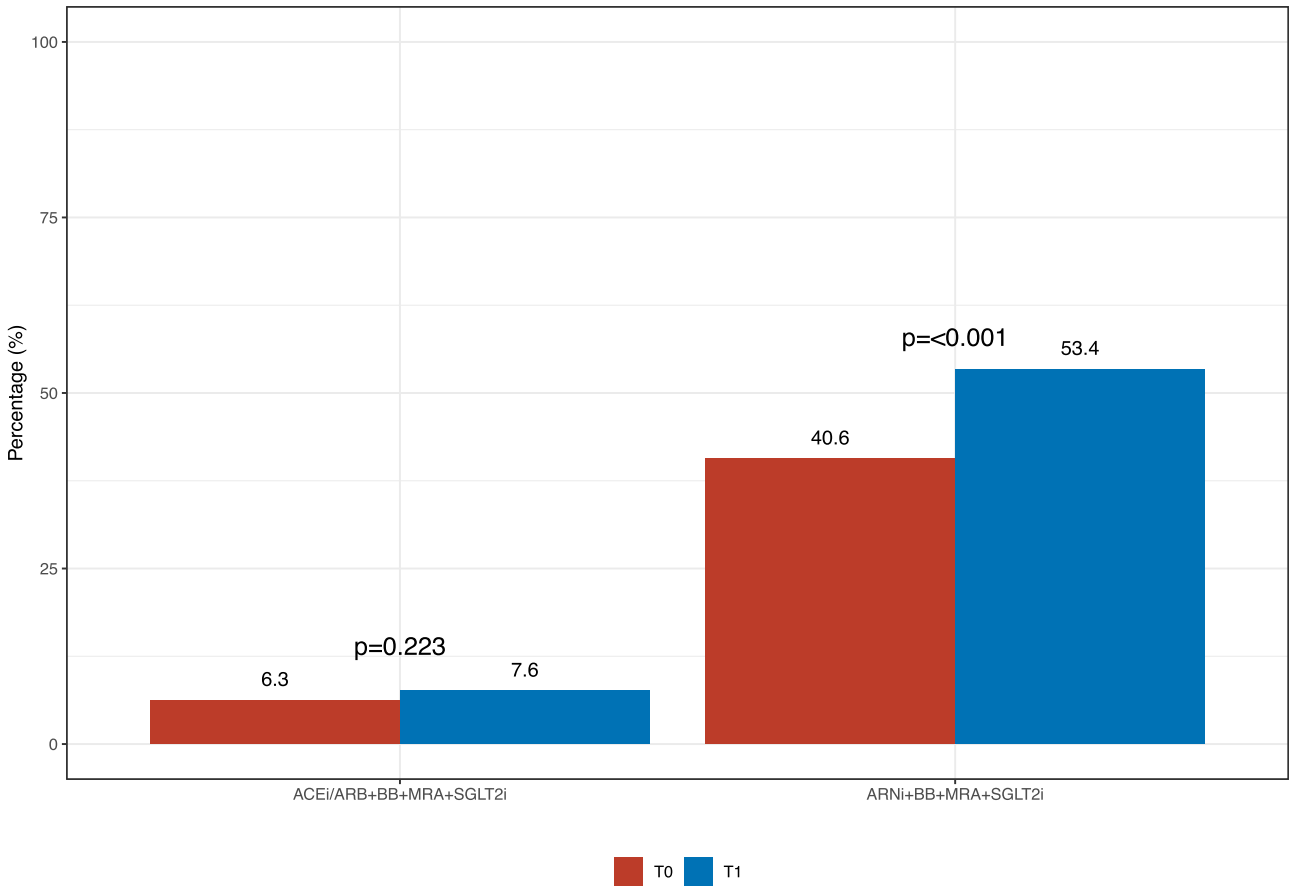


Fig. 3. Differences in prescription rates of 4-drugs combinations between T0 and T1. Bar graph showing differences in the percentage of HFrEF patients taking all 4 drug classes between T0 (red) and T1 (blue). P-values were adjusted for multiple comparisons using the Holm-Bonferroni method. *ARNI, Angiotensin 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.*

circulation among health professionals (8). An analysis from Jankowska et al. (9) showed that, in the setting of HF, the most frequently mentioned barriers to the application of guideline-recommended pharmacological therapy by healthcare professionals were treatment side effects and intolerance. Also in this context, a structured educational activity could be useful to improve adherence to guidelines and to reinforce awareness on an informed use of drugs. In our analysis, we observed a reduction in the proportion of patients non-treated with SGLT2i and ARNI, despite no specific contraindications to these drugs, showing how implementation strategies, particularly guidelines dissemination and debate on specific clinical cases, might be useful to overcome common barriers to the optimization of HF treatment. Our analysis showed no substantial variations in the proportion of patients receiving ≥50% of the target doses recommended by the European Guidelines, which is a common finding in international registries. Even if treatment initiation should be highlighted over treatment dose optimization, when all the foundational HFrEF drugs are initiated, dose titration should be implemented according to patient profiles. Cowie et al. reported an analysis of the QUALIFY registry (10) showing, in a total of 7095 HFrEF patients from 549 centers in 36 countries worldwide, a high proportion of patients on treatment with the individual drugs; nevertheless, most patients did not receive target doses of recommended therapies, at any point during the 18-month follow-up. Furthermore, a recent Scientific Statement of the Heart Failure Association of the ESC on therapeutic inertia in HFrEF management, reported that in all most large and recent HF registries worldwide only minority of enrolled patients reached the target dose for both RAASi/ARNI (17–40%) and beta-blockers (13–40%), also proposing practical strategies to reach/maintain optimized doses (11). Thus, drugs titration remains challenging in the management of the disease and specific and structured implementation strategies are needed in this setting.

5. Limitations

Several limitations should be acknowledged for this study. First, the observational, non-randomized design of the study and, especially, the absence of a contemporaneous control group to verify the study results, prevents causal attribution of the observed treatment implementation solely to the educational intervention, as the observed improvement may be partly explained by natural trends, including the progressive adoption of HF foundational drugs in routine practice. Second, the retrospective nature of the T0 phase may have introduced selection and information bias, and consecutive enrolment could not be independently verified. Third, participating sites were mainly specialized HF outpatient services, often tertiary referral centers, which may limit generalizability to other care settings. Fourth, the cross-sectional data collection did not allow assessment of treatment sequence, timing, or titration attempts, and clinical outcomes, safety or tolerability were not evaluated, thus implications of improved prescription patterns on patient prognosis remain speculative. Fifth, baseline differences between the retrospective and prospective cohort may have act as potential confounders affecting prescribing patterns, however this issue was partly solved by a comparative analysis of a subgroup of patients with available data at both assessments (T0 and T1) showing a significant increase in prescription rates of ARNI, MRA, and SGLT2i, and a favorable balance between treatment initiation and discontinuation and by an adjustment of

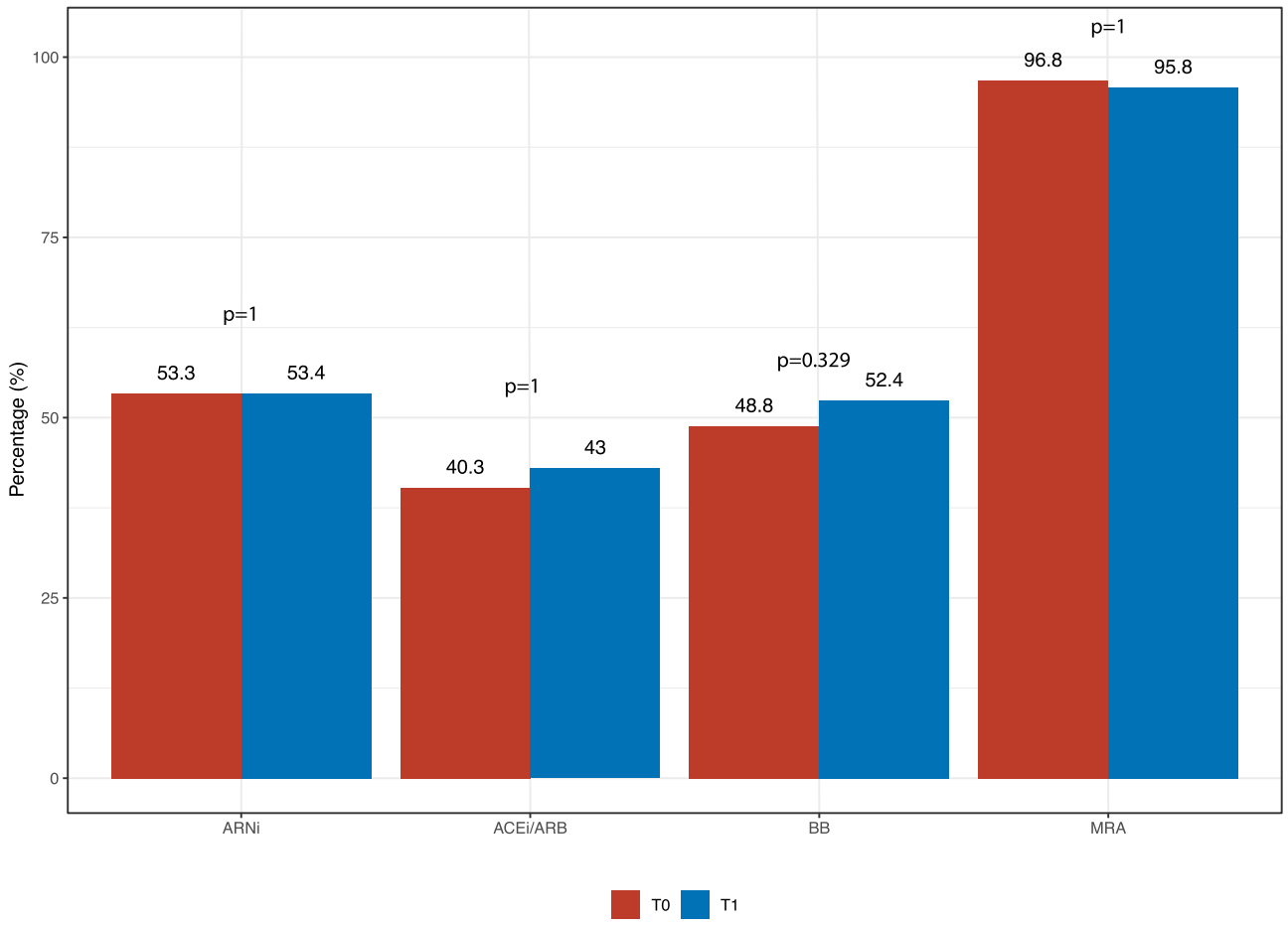


Fig. 4. Differences in prescription rates of HFrEF drugs doses between T0 and T1. Bar graph showing differences in prescription rates of intermediate–high doses (≥50% of target dose) of HFrEF drugs between T0 (red) and T1 (blue). P-values were adjusted for multiple comparisons using the Holm-Bonferroni method. *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.*

all analysis for multiple comparisons using the Holm-Bonferroni method. Finally, no data on vericiguat use were collected for the present analysis and a focused data collection is now ongoing.

6. Conclusions

In patients with HFrEF treated in real-world clinical practice, there is an ongoing need to optimize prescription of guideline-recommended therapy with a particular focus on combination strategies and foundational drugs titration over time, that still represent relevant gaps in disease management. Educational activities represent a simple and feasible strategy to support clinicians, associated with improved prescription patterns and closer adherence to guideline-recommended therapy.

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Declaration of competing interest

The authors have no competing interests to declare.

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Supplementary materials

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