Patient adherence to drug treatment in a community based-sample of patients with chronic heart failure

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1. Introduction

Despite high success in heart failure (HF) treatment, prognosis of patients with HF seems to be improving slowly [1–3]. In real world, there is an increasing divergence between prescriptions of HF medication and guideline recommendations [4–7]. However, few detailed data provides a granular representation of reasons for under-use of HF drugs in HF patients with reduced ejection fraction (HFrEF). Interestingly, recent observational studies pointed out that prescriptions of evidence-based treatment continue to be representative also in HF patients with preserved ejection fraction (HFpEF), in spite of a lack of clear benefits [6,8]. However, observational data suggested a potential benefit among heterogeneous HFpEF settings [9,10].

Beyond physicians' prescriptions, patient adherence remains an open research field. This issue may be particularly relevant in chronic HF (CHF) patients, wherein the inability to tolerate drug treatments might lead to a poor uptake of HF medications. Another aspect that needs to be explored is the prognostic impact of patient adherence to HF drugs as prescribed by physician, even when optimal therapy and target dose are rarely achieved. Indeed, a deep knowledge of the real use of evidence-based medications assessed through patient adherence might better clarify if medical therapy, with a range of doses used in clinical practice, represents patients' needs and drug tolerability in real-world setting.

Thus, in an unselected cohort, we sought to evaluate current practice-based management of CHF regarding pharmacological administration of renin-angiotensin system inhibitors (RASi), beta-blockers (BB) and mineralocorticoid receptor antagonists (MRA). Further, rate and prognostic impact of patient adherence on medical HF therapies as prescribed by the treating physician were evaluated.

2. Methods

2.1. Data source

The methods have been previously published [11–13]. Briefly, HF outpatient data was retrieved from Trieste Observatory of Cardiovascular diseases (northeast of Italy), an ongoing prospective, observational longitudinal community dataset. This registry has established a population-based database in which administrative data and clinical information are integrated. The e-Chart, including medical information collected by cardiologists during routine clinical practice, is linked with data drawn from clinical consultations, instrumental procedures, laboratory analyses and prescribed treatments. The e-Chart is also integrated into a regional Data Warehouse that includes regional databases such as the Registry of Deaths, Hospital Discharge, the District Healthcare Services (intermediate and home care), Public Laboratories and Public Drug Distribution System [11–13]. This HF population was representative of patients seen by HF specialists. To protect privacy, information retrieved from the different databases are linked via a single anonymous identification code by institutional technical staff. The reverse process is not possible since the generation code table is not available to the authors. The institutional ethical board approved the study. In line with the hospital administration policies of the institutional review board, an informed consent was obtained.

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2.2. Study design and clinical variables

Between November 2009 and December 2015, consecutive HF patients were considered. HF patients without any available value of left ventricular ejection fraction (LVEF) and NYHA class were excluded. The end of the follow-up was set on December 31, 2016 (data extraction). For the identification of HF patients, clinical findings compatible with HF were selected from the e-Chart. We implemented the data of the e-Chart with discharge codes of previous hospitalizations based on the nomenclature of the International Classification of Diseases-Ninth Revision (ICD-9-CM), available laboratory data, interventional procedures, and prescribed treatments. Further, to retrieve the cause of hospitalizations, five years preceding the index visit was considered. We focused on prescribed HF medication including RASi, BB, and MRA in patients with LVEF<40%. Drugs prescription was also analyzed in patients with LVEF≥40%. Although the post-hoc analysis of clinical trials of these drugs suggested potential benefits in patients with mid-range LVEF (40-49%), at time of study, the guidelines recommendation was less robust among these patients. Thus, mid-range of LVEF was included in the group of preserved LVEF. Based on drugs prescriptions, patient adherence was evaluated according to LVEF. To estimate a non-cardiac co-morbidities load, the sum of 15 comorbidities were considered [11,13]. Paroxysmal, persistent or permanent type of atrial fibrillation were considered together if documented in the history or at enrolment ECG.

2.3. Drugs prescriptions

The rate and dosage of four classes of medications at index visit was considered. Specifically, pharmacological treatment was defined as follows: 1) rate of prescriptions (if not contraindicated or intolerant) of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) (i.e., RASi), BB and MRA; 2) due to its prognostic significance [14], prescription dosage is given at least ≥50% of the target dosage for all the prescribed drugs [5,14]. Patients' intolerance and/or contraindications as indicated by the treating physician were recorded. The contraindications and intolerance of the drugs were identified by the presence of a specific flag "Intolerance to drug X" as recorded in e-Chart (Cardionet®). To avoid a possible diagnostic underestimation of contraindications, we implemented the data of the E-Chart with discharge codes of previous hospital access (i.e., COPD), interventional procedures for HF patients (i.e., procedures for peripheral artery disease (PAD)), and laboratory analysis (i.e., glomerular filtration rate). The heart rate and arterial blood pressure measure at time of clinical evaluation were also considered. Subsequently, drug-specific intolerance was considered. Particularly, intolerance to RASi was considered, taking into account one of the following criteria: CKD-EPI GFR < 30 ml/min/1.73 m2, K > 5 mmol/l and systolic blood pressure (SBP) <100 mmHg. Whereas the presence of COPD/asthma, heart rate < 60 bpm, SBP < 100 mmHg, PAD, and NYHA IV were considered for BB intolerance. To identify the MRA intolerance, potassium > 5 mmol/L and CKD-EPI GFR < 30 ml/min/1.73 m2 were considered. When the reason for non-prescriptions was identified, ESC guidelines at the time of recruitment were also considered. Therefore, for patients recruited within 2016, non-indication for MRA was evaluated. Specifically, MRAs were identified as "not indicated" in patients presenting one of the following criteria: NYHA 1, LVEF>35%, not under treatment with ACEi/ARB, BB. Patients without a prescription at the index visit and presenting at least one prescription in the two years before the index visit were considered as intolerant (since the prescription was no longer confirmed by the cardiologist at the index visit). The contraindications were defined according to ESC guidelines at time of recruitment [15–17].

2.4. Patient adherence

All prescriptions dispensed to the cohort members during follow-up from the public drugs distribution system were identified. The period covered by an individual prescription was calculated by dividing the total amount of the drug prescribed by the daily dose as prescribed by cardiologists (during the last visit before the drug prescription). For overlapping prescriptions, it was supposed that the patient had completed the former one before starting the second one. Adherence to drug treatment, defined as Patient-adherence, was assessed as the cumulative number of days in which the medication was available divided by the days of overall follow-up, a quantity referred to as "proportion of days covered" (PDC) [18] (Supplementary Fig. S1). Patients were considered adherent if they observed at least ≥75% PDC value of their drug treatment schedule. Patients prescribed more than one drug class had to spend more than 75% of their follow-up covered by prescriptions with all the drugs to be classified as adherent. This cut-off value was chosen because this adherence level to antihypertensive drug treatment showed a clear association with a reduction of cardiovascular outcomes and mortality in previous Italian studies [19,20]. However, to overcome the arbitrary nature of this categorization, in a secondary analysis we used more permissive (70%) and more restrictive (80%) categories of PDC to define adherence. The patient adherence for each drug class was calculated from the index visit (or when that drug was prescribed by the cardiologist for the first time during follow-up) until the end of follow-up (or when that drug was no longer prescribed by the cardiologist).

2.5. Study endpoint

The outcome was the composite endpoint of death and HF hospitalization. HF hospitalization was defined using ICD-9-CM codes for HF (428.x) and hypertensive HF (402.01, 402.11, 402.91).

2.6. Statistical analysis

Summary statistics of the clinical and instrumental variables at the index visit were expressed as median (interquartile range), or counts and percentage, as appropriate. Comparisons between LVEF groups for continuous variables were performed with the Mann-Whitney test. The Chi-square, or Fisher exact test, was calculated for categorical variables. A Cox proportional-hazards model was fitted for the composite endpoint of HF hospitalization and death, including a list of covariates based on clinical relevance. The proportional hazard assumption for the time-fixed covariates was tested by means of Schoenfeld residuals [21]. Because adherence to drug treatment may change over time, it was inserted in the model as a time-dependent variable. The final model included demographic (age, sex), medical history (atrial fibrillation, previous HF hospitalization, number of drugs), etiology (ischemic disease), co-morbidities load (number of non-cardiac co-morbidities ≥3), LVEF groups, NYHA class, CKD-EPI GFR, and use of diuretics, ACEi/ARB, BB and MRA. In addition, the interaction term between adherence to drug therapies and LVEF group was included in the model. This analysis was performed by excluding patients who did not receive any prescriptions of the drugs of interest at the index visit (based on the assumption that for these individuals drug treatment might not be indicated) and those who did not reach at least six months of follow-up (to have at least 6 months of potential exposure to the drugs of interest).

The Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA) was used for the analyses. For all hypotheses tested, two-tailed p values less than 0.05 were considered to be significant.

3. Results

A total of 3424 CHF patients were identified, and 2528 patients met the selection criteria (Supplementary Fig. S2). Of these, 609 (24%)

presented LVEF<40%, whereas 1919 (76%) presented a LVEF≥40%. Clinical characteristics of the study population according to LVEF groups are reported in Table 1. The mean age was 76 years, 42% were women. About half of the HF population had ischemic heart disease as the underlining cause of HF. There was a significant background of hypertension and history of atrial fibrillation. Three quarters of the HF population presented ≥3 non-cardiac comorbidities, and approximately one quarter of patients had a previous HF hospitalization.

In comparison to patients with LVEF≥40%, HFrEF group presented high proportion of male with significantly more patients having ischemic heart disease. Whereas, atrial fibrillation, hypertension, and obesity were less frequently observed in HFrEF than those HFpEF patients (Table 1).

3.1. Drug treatment in the overall population and patients with LVEF < 40%

Overall, 77%, 63% and 33% of patients received prescriptions of RASi, BB, and MRA respectively (Table 1). Considering patients with LVEF<40%, rate of prescriptions of RASi, BB, and MRA was 84%, 70%, and 40%, respectively (Table 1 and Fig. 1). Table 2 reports the combinations of prescriptions of these drugs for the overall population and according to LVEF. Overall, the combination of BB and RASi was prescribed to 1292 patients (51%), while BB and RASi were combined with MRA in 541 (21%) and 636 (25%), respectively. Less than one-third of the HF patients received triple therapy (26% of HFrEF patients), and 63% of HFrEF patients received a combination treatment of RASi/BB (Table 2).

Considering target dosages, a clear and significant under-treatment for all medications was observed (Fig. 1, Panel B). This trend was more pronounced when we considered drug combinations, achieving a prescription of triple therapy at target dose only in 4% of CHF patients (Supplementary Fig. S3). 54% of HFrEF patients were without indication for MRAs.

For RASi and BB, the reported contraindications or documented intolerances were the main reasons for non-prescriptions. Considering contraindications/intolerance, the real rate of under-treatment in patients with LVEF<40% was 5%, 9%, 7% for RASi, BB, MRA respectively (Fig. 1, Panel A). Supplementary Table S1 further shows specific contraindications and/or intolerances of these drugs. In patients with HFrEF, high potassium level and advanced renal disease were the most frequent contraindications for RASi, whereas COPD/asthma and peripheral artery disease emerged as the most frequent reason for non-prescription of BB.

3.2. Medical treatment of patients with LVEF≥40%

In patients with LVEF≥40%, RASi were prescribed most frequently (75%), followed by BB (61%), and MRA (30%). Prescription rates significantly differed from the HFrEF group, however, differences were relatively small (Fig. 1, Panel A). When a target dose was considered, patients with LVEF≥40% presented a higher proportion of patients at target dose for RASi and BB than those with LVEF<40% (Fig. 1, Panel B). Concordantly, there was a lower proportion of contraindications for RASi and BB in patients with LVEF≥40% than those of their LVEF counterparts (Supplementary Table S1). As expected, the rate of non-prescriptions without contraindications or intolerances was higher in patients with LVEF≥40% (Fig. 1, Panel A).

3.3. Patient adherence and adverse outcome

At 1-year, 38% of patients resulted as adherent to drug treatment as prescribed by the treating physician (31% in patients with LVEF<40% *vs* 41% with LVEF≥40%). Fig. 2 shows the proportion of adherent patients according to the prescribed drugs, alone or in combination. Higher rates of adherence were observed among patients receiving 1-drug

Table 1
Clinical characteristics of the whole HF population as well as according to LVEF.

Variable	Study cohort (2528)	LVEF		*p*-Value
		<40% (609, 24%)	≥40% (1919, 76%)	
Age, median (IQR), years	76 (70-82)	74 (67-81)	77 (70-82)	<0.001
Gender, male, n. (%)	1470 (58)	441 (72)	1029 (54)	<0.001
NYHA III-IV, n. (%)	338 (13)	100 (16)	238 (12)	0.011
NT-proBNP, median (IQR), pg/ml[a]	386 (187-728)	640 (351-1134)	297 (154-566)	<0.001
SBP, median (IQR), mmHg	130 (120-145)	130 (120-140)	130 (120-150)	0.263
Heart Rate, median (IQR), beats/min	71 (64-84)	71 (64-80)	71 (63-81)	0.174
Heart Rate < 70 bpm, n. (%)	1049 (41)	253 (42)	796 (41)	0.954
eGFR, median (IQR), ml/min/1.73 m^2	61 (45-77)	60 (42-78)	62 (45-77)	0.539
Sodium, median (IQR), mmol/l	139 (137-141)	139 (137-141)	140 (137-142)	0.040
Potassium, median (IQR), mmol/l	4.2 (3.6-4.6)	4.2 (3.6-4.7)	4.2 (3.6-4.6)	0.352
Hemoglobin, median (IQR), g/dl	12.9 (11.5-14.2)	13.2 (11.8-14.6)	12.8 (11.4-14.1)	<0.001
Ischemic disease, n. (%)	1209 (48)	376 (62)	833 (43)	<0.001
Atrial Fibrillation, n. (%)	1341 (53)	265 (44)	1076 (56)	<0.001
Hypertension, n. (%)	2026 (80)	456 (75)	1570 (82)	<0.001
Body mass index, median (IQR), kg\m^2	26 (24-30)	25 (23-28)	27 (24-30)	<0.001
Obesity, n. (%)	587 (23)	88 (14)	499 (26)	<0.001
Diabetes Mellitus, n. (%)	975 (39)	241 (40)	734 (38)	0.559
Peripheral vascular disease, n. (%)	674 (27)	159 (26)	515 (27)	0.723
Chronic Kidney disease, n. (%)	1317 (52)	335 (55)	982 (51)	0.099
COPD/Asthma, n. (%)	846 (34)	194 (32)	652 (34)	0.334
Anemia, n. (%)	981 (39)	209 (34)	772 (40)	0.009
Liver Disease, n. (%)	123 (5)	35 (6)	88 (5)	0.246
Cancer, n. (%)	353 (14)	77 (13)	276 (14)	0.281
Dementia, n. (%)	37 (1)	11 (2)	26 (1)	0.419
Rheumatic disease, n. (%)	117 (5)	22 (4)	95 (5)	0.171
Peptic ulcer disease, n. (%)	82 (3)	18 (3)	64 (3)	0.645
Cerebrovascular accident, n. (%)	375 (15)	93 (15)	282 (15)	0.728
Charlson comorbidity index ≥3, n. (%)	1940 (77)	480 (79)	1460 (76)	0.164
Number of comorbidities ≥3, n. (%)	1687 (67)	384 (63)	1303 (68)	0.047
Previous HF hospitalization, n. (%)	847 (33)	259 (43)	588 (31)	<0.001
ICD, n. (%)	125 (5)	92 (15)	33 (2)	<0.001
CRT, n. (%)	38 (2)	25 (4)	13 (1)	<0.001
Number of drugs ≥5, n. (%)	1682 (67)	424 (70)	1258 (66)	0.003
Diuretics, n. (%)	1949 (77)	462 (76)	1487 (77)	0.405
ACEi/ARB (monotherapy + combination therapy), n. (%)	1944 (77)	509 (84)	1435 (75)	<0.001
Beta-blockers (monotherapy + combination therapy), n. (%)	1603 (63)	424 (70)	1179 (61)	<0.001
MRAs (monotherapy + combination therapy), n. (%)	827 (33)	242 (40)	585 (30)	<0.001

ACEi: Angiotensin-Converting Enzyme inhibitors; ARB: Angiotensin II Receptor Blockers; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; eGFR: estimated Glomerular Filtration Rate; HF: Heart Failure; ICD: Implantable Cardioverter Defibrillator; IQR: Interquartile Range; LVEF: Left Ventricular Ejection Fraction; MRAs: Mineralocorticoid Receptor Antagonist; NYHA: New York Heart Association; SBP: Systolic Blood Pressure.

[a] 1471 out of 2528 have the NT-proBNP value missing.

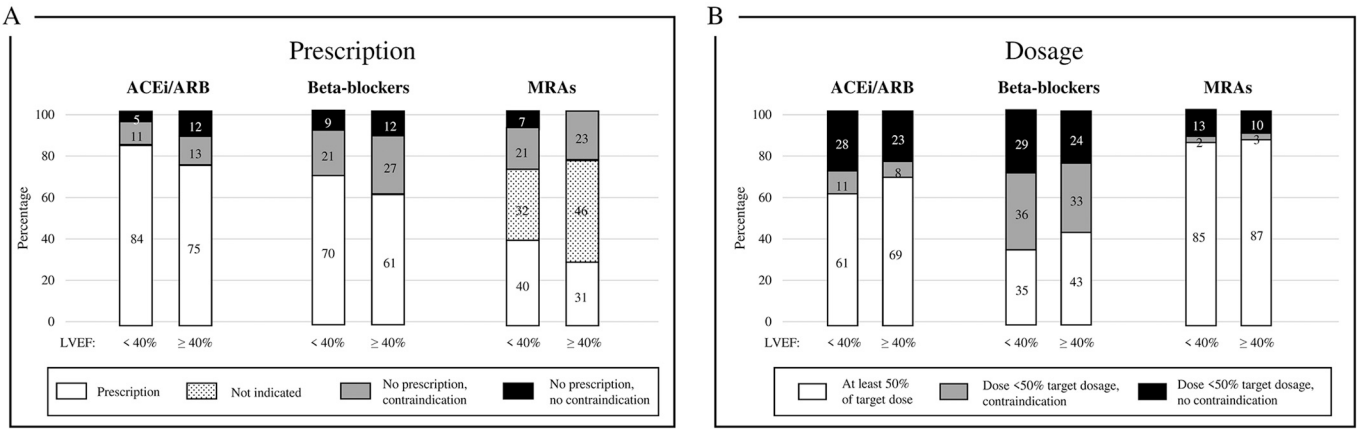

Fig. 1. Proportions of prescriptions (panel A) and prescription dosage at least ≥50% of the target dosage (panel B) for angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRAs) according to LVEF.

Table 2
Combinations of treatments prescriptions at the index visit.

Drugs	Overall N (%)	LVEF < 40% N (%)	LVEF ≥ 40% N (%)	P-Value
None	190 (8)	44 (7)	146 (8)	0.755
ACEi/ARB + Beta-blockers	1292 (51)	381 (63)	911 (47)	<0.001
Beta-blockers + MRAs	541 (21)	176 (29)	365 (19)	<0.001
ACEi/ARB + MRAs	636 (25)	213 (35)	423 (22)	<0.001
ACEi/ARB + Beta-blockers + MRAs	433 (17)	160 (26)	273 (14)	<0.001

ACEi: Angiotensin-Converting Enzyme inhibitors; ARB: Angiotensin II Receptor Blockers; LVEF: Left Ventricular Ejection Fraction; MRAs: Mineralocorticoid Receptor Antagonist.

prescription (61% RASi, 54% BB and 38% MRA) than those patients taking the combination drugs. Specifically, only 15% of patients who received the triple combination therapy emerged as adherent (Fig. 2).

The incidence rate of the composite outcome was significantly higher in patients with LVEF<40% than those patients with LVEF≥40% (at 4 years, 55.8% vs 46.7%, respectively, $p < 0.001$) (Supplementary Fig. S4). At multivariable Cox regression model, patient adherence was associated with a significantly lower risk (15% risk reduction, $p = 0.041$) of the composite endpoint of HF hospitalization and death (Supplementary Table S2). This was also confirmed by using more permissive (70%) and more restrictive (80%) categories of PDC (hazard ratio: 0.83, 95% confidence interval: 0.71-0.97, and 0.84, 0.71-0.99, respectively).

4. Discussion

The current analysis provides a clear picture of the practice-based management of RASi, BB, and MRA in an unselected cohort of CHF patients. Current analysis shows that: (i) rate of drug therapies was in line with previous observations derived from selected HF cohorts of the cardiology registries [1,5,6,15,22]; (ii) in the HFrEF population, downward trend in prescription rate for evidence-based HF therapy was evident where combination therapy and target dose was evaluated; (iii) LVEF≥40% group presented small difference in drug prescriptions from those patients with LVEF<40%; (iv) patients' adherence to HF medication as prescribed by the treating physician resulted as unsatisfactory for both LVEF groups; (v) good patient adherence to physicians' prescriptions was associated with a better prognosis regardless of HF type.

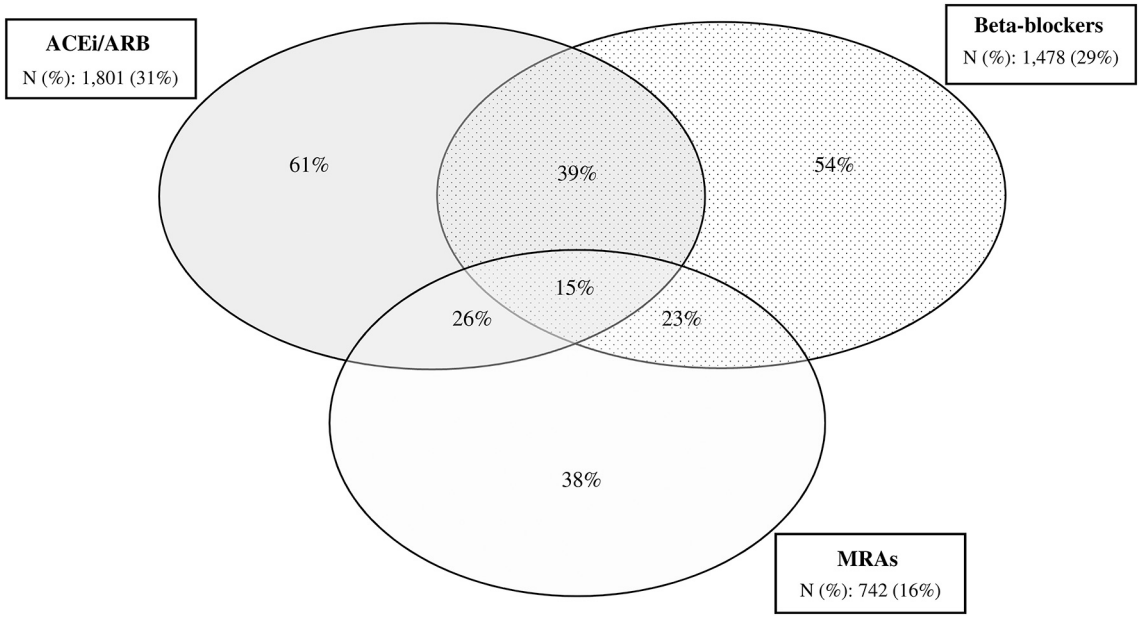

Fig. 2. Proportions of patient-adherence at least ≥75% PDC value of their drug treatment during the first year of follow-up.

According to previous studies of HF patients with LVEF<40% [15,23,24], the real treatment rate was satisfactory. However, there was a frequent failure to reach target doses. Still, our data remains in line with previous findings that unanimously indicated an under-treatment where target doses are considered [1,5,6,15,22]. In the current analysis, under-doses were especially relevant when a combination of drugs was administered, wherein a triple therapy at target dose was prescribed to only 4% of patients with LVEF<40%. Lower prescriptions of combined therapy and tolerant dosage may be attributed to several limiting factors characterizing our population. Particularly, high average age and high comorbidities burden may contribute to suboptimal treatment of HFrEF patients. However, these characteristics resemble a real-life in which an age-related factors and polypharmacy may contribute to suboptimal therapy of HF patients.

Despite a lack of clear evidence of HF treatments reducing mortality in HFpEF patients, we found that the prescriptions rates of HF therapy were quite similar to patients with LVEF<40%. This confirms a gap between current recommendations and clinical practices [4,6,25]. Indeed, the European Society of Cardiology Heart Failure Long-Term Registry reported similar results, although the recruited patients were younger and more often male than those of our cohort [25]. Interestingly, a similar trend also emerged from CHECK-HF registry enrolling unselected elderly HF patients [8]. Together with our results, these findings may underline that evidence-based drugs have not convincingly shown to have a neutral effect on outcomes in patients with LVEF≥40%. It is also suggested that these HF drugs continues to be required for the management of underlining heart disease in a high proportion of HFpEF patients.

4.1. Patient adherence

In our population, there was a large gap between the physicians' prescriptions and patient adherence. Despite evidence of large between clinical practice and 'optimal medical therapy', little data exists regarding patient adherence to drug treatments in the HF population. The reported analysis highlights that the estimation of 'under-treatment' requires an assessment that is not limited to physicians' prescriptions. More specifically, poor patient adherence was observed when combination therapy was prescribed, highlighting patient non-adherence goes hand in hand with polypharmacy. This is in line with previous findings, wherein a high percentage of patient non-adherence occurred, especially when polypharmacy had administrated [26]. Previous studies addressing this issue considered administrative data and based the patients' adherence estimation on the "defined daily dose" metric [27]. This procedure might not capture the real patient needs and may lead to an under/overestimation of patient adherence. Whereas, we considered physician prescription doses and reported detailed clinical information and reasons for non-prescription, thereby exploring the real patient tolerability. Furthermore, previous observations had considered the HF population regardless of LVEF [26,28]. Since there are different implications for evidence-based therapy in HF, in the current study patient adherence according to LVEF type was considered. When prognostic implications were explored, patient adherence to drug prescriptions resulted in a better outcome. Of note, the impact of patient adherence remains significant even if a lower prescription dose emerged. This finding deserves several considerations. Particularly, our observation may support the revised of our approach to optimal HF medical therapy. Although the efficacy of low doses has not been addressed, our data might advocate a reflection on accepting lower, age-adjusted, target doses of HF medication in a setting where an "optimal therapy" may not be achieved. As elegantly reported by Tavazzi et al. [29], we do not truly know the optimal dose for any patient and target effect should be persuaded in real-life. Again, the impact of patient adherence occurred irrespective of HF type. This has important implications and may support a potential benefit from disease-modifying therapy in the heterogeneous spectrum of HFpEF syndrome. In this sense, our analysis, along with previous studies addressing the benefit of these drugs in HFpEF real-life setting [9,10], should be an effort for future trials strategies to differentiate the clinical situations in which HFpEF patients might benefit from available treatment.

The gap between the drugs prescribed and patient adherence also underlines how the current medical record system may result in incomplete knowledge about treatment in clinical practice. In this respect, it is important to recognize that the primary source of the integrated clinical and administrative database, incorporating drug prescriptions and purchases, may represent a huge opportunity for the healthcare system to optimize patient treatment and clinical management. As underlined by the authors of CHECK-registry [6], a better understanding of patients' barriers to adopt of evidence-based therapies would have tremendous public health benefits by designing effective quality improvement interventions, which could translate into the improvement of prognosis.

4.2. Limitations

There are several limitations to the current study. First, a limited geographic area may prevent the application of this data to other areas, which in turn, may differ for socioeconomic and healthcare provider standards. Additionally, adherence was derived from drug prescriptions, a widely used method which, however, requires the assumption that the proportion of days covered by a prescription corresponds to the proportion of days of drug use.

All HF patients who had a cardiological evaluation were included in our study, regardless of the previous history of the disease or drug treatment use. This approach may lead to a form of selection bias since the patients have by definition survived until the index visit. In addition, this prevents us from investigating the complete sequence of outcomes experienced and drug treatments supplied after the diagnosis of HF. It was also not possible to assess the initial LVEF and estimate patients with improved LVEF. Another limitation is the absence of socioeconomic information that may have an impact on patients' adherence; otherwise, dedicated future studies are encouraged on this topic. Of note, contraindications/intolerance were considered at the index visit but the new potential contraindications/intolerances should also be considered during follow-up. Since drug therapies are usually stopped in patients with advanced HF and a worse prognosis, this may be an important aspect for future studies.

4.3. Conclusion

In an unselected cohort of CHF patients, when the reasons for non-use are taken into account, the rate of recommended drug prescriptions can be considered satisfactory in patients with HFrEF, albeit target doses and triple therapy remain lower than recommended. In the LVEF≥40% group, prescription of HF medication was consistent with a small difference from patients with LVEF<40%. Importantly, there was a significant gap between drugs prescriptions and patient adherence, highlighting that drug treatments remain largely sub-optimal when patient adherence is concerned. Also, patient adherence to prescribed medication exhibited a prognostic role irrespective of HF type. As such, patient adherence seems to be crucial for estimating the real under treatment in clinical practice and essential for patient improving HF prognosis.

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Author statement

All authors take responsibility for all aspects of the reliability and

freedom from bias of the data presented and their discussed interpretation.

Declaration of Competing Interest

All authors declare that they have no conflict of interest to disclose.

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