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Adherence to Disease-Modifying Therapy in Patients Hospitalized for HF: Findings from a Community-Based Study

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Abstract

Background. Previous studies of polypharmacy (PP) for Heart Failure (HF) patients were based on surveys of highly selected populations and methods for estimating adherence in PP have widely varied. Moreover, adherence has been evaluated only in terms of physician's prescriptions.

Aim. Describe pharmacological guidelines compliance in a real-world HF cohort based on effective patient's drugs purchases and estimate the impact of PP adherence on survival.

Methods and Results. Between 2009 and 2015, patients hospitalized with a HF diagnosis and with at least one purchase post-discharge of angiotensin-converting enzyme inhibitors, ACE, or angiotensin receptor blockers, ARB, or beta-blocking, BB, or anti-aldosterone agents, AA, were recruited from an administrative database. Adherence was evaluated using two measures (Proportion of Days Covered, PDC, Medical Possession Ratio, MPR). A new measure of PP adherence was introduced, the Patient Adherence Indicator (PAI). A Cox model was estimated to quantify impact of PAI on survival. The most common drug combination was ACE/ARB and BB (58.1%) and the less frequent was ARB and AA (11.5%). Triplet ACE/ARB, BB and AA was purchased at least once by 27.3% of patients. Mean daily dosages were inferior to the target dosages for all drugs. From 41% to 58% of patients showed a poor poly-adherence measured by the PAI index.

Conclusions. Patients assume daily doses lower than the target dosages. PDC and MPR showed differences related to the specific drugs classes but were not prognostically different when combined into the PAI index. Adjusting for patient's characteristics and intermediate events, PP non-adherence was significantly associated with lower survival.

Keywords Heart Failure (HF); Adherence; Proportion of Days Covered (PDC); Medical Possession Ratio (MPR); Administrative Health Data.

1. Introduction

Heart failure (HF) is a major and growing public health issue, characterized by steep morbidity and mortality rates, and high costs [1]. Despite the advances in the understanding of the pathophysiology of chronic HF and the improvement therapy, HF mortality and morbidity rates remain high [2,3]. Current HF

guidelines [4,5] have consistently focused on the benefits of neurohormonal therapy in HF patients to delay progression and improve survival. These recommendations also underlined up-titration of neurohormonal doses toward target, when possible, by the time of hospitalization discharge. However, medication nonadherence is a common issue, and it is associated with adverse health conditions and increased economic burden to the healthcare system especially in case of chronic diseases such as HF [6]. Recent observations suggest that up to 50% of early post discharge mortality may be associated with guideline nonadherence [7].

Previous epidemiological studies of polypharmacy (PP) adherence [8] have mainly been based in HF patients on surveys of highly selected populations [9] and on physicians prescriptions [10,11], thus no current data are available on HF patients adherence based on effective purchases of drugs in a real world setting. Furthermore, methods for estimating patient's adherence in PP have varied and often have been not evaluated in detail. Again, most of the previous results based the estimation of PP adherence only on medical prescriptions at discharge and not on successive purchases and adherence patterns [11].

Hence, the present study aim was to describe patients' adherence to disease-modifying therapies, including the evaluation of target dosages based on drug's purchases, among patient discharged with a HF diagnosis. In particular, adherence to treatments was evaluated by estimating adherence in the first year after discharge from an episode of HF hospitalization. Further, we proposed a new measure of PP adherence by computing the ratio between two quantities: the "Poly-adherence" (PA) and the "Purchase Indicator" (PI), so producing the Patient Adherence Indicator (PAI). Finally, the prognostic impact of adherence to PP therapy on survival was also estimated.

2. Materials and Administrative Data

2.1 Study setting

Between January 2009 and December 2015, patients hospitalized in the Friuli Venezia Giulia Italian Region (FVG, a north-eastern region of Italy, with a population of about one million and two hundred thousand inhabitants) with a first diagnosis of HF and at least one pharmacological purchase of disease-modifying drugs for HF were recruited. Patients who were not inhabitants of the FVG region or were younger than 18 years at the time of hospitalization were excluded. Enrollment occurred from data of discharge of HF hospitalization.

2.2 Data sources

The data of healthcare administrative archives were used for identification of HF patients. Indeed, the FVG regional Data Warehouse includes various sources of data, such as the Registry of Births and Deaths, Hospital Discharge, the District Healthcare Services (intermediate and home care), Public Laboratories and Public Drug Distribution System. Of note, the availability of laboratory analyses performed in public hospitals is a peculiar characteristic of this Region. Each record in the dataset was related to an event, which could be an HF hospitalization or hospitalization for other causes, an activation of Intermediate Care Unit (ICU) service or an Integrated Home Care (IHC). For all these events (admission to hospital or ICU/IHC), we collected dates of admission and discharge. Moreover, for each HF hospitalization, we identified with a binary flag if the patient was discharged from a Cardiological Ward (CW) and if a cardiological visit was performed within 24 months previous the hospitalization. For pharmacological prescriptions, each record represented a pharmacological purchase characterized by the date of acquisition, ATC (Anatomical Therapeutic Chemical classification system) and AIC codes (authorization code related to Italian market) and the total number of purchased boxes.

2.3 Study population

HF primary diagnosis included ICD-9CM codes for HF (428, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91 and 404.93) selected according to the National Outcome Evaluation Program. In order to limit underestimation of comorbidities, diagnostic discharge codes of the pre-period study window from 2004 to 2008 (*Figure 1*) were considered. Previous cardiological visits (as recorded in administrative records) were searched within two-years from the index HF hospitalization.

An index date of the first HF discharge in the study period from January 2009 to December 2015 was considered, and those patients who died during the first HF hospitalization were excluded. Since the impact of adherence was considered on survival outcomes having at least one year of observation available, patients who survived at least one year after discharge were selected. Finally, only patients with at least one pharmacological purchase related to the disease modifying drugs were included [4] (*Figure 2*). Specifically, we considered the following drugs: angiotensin-converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB) - these two considered as a unique class- ACE/ARB, beta-blocking (BB) and anti-aldosterone agents (AA).

Patients were classified as Worsening Heart Failure (WHF) or De Novo on the basis of the presence of at least one HF hospitalization in the 5 years preceding the index HF hospitalization (*Figure 1*). The study-period was divided into the observation period (365 days from the index discharge date) and only patients alive at the end of the observation period were followed up to observe survival outcomes (*Figure 1*).

Demographic, comorbidities, procedures and laboratory tests performed during hospitalization were considered. Finally, the Charlson Comorbidity Index [12] was computed using hospital diagnoses based on ICD-9CM that occurred within five years before the hospitalization and integrated with laboratory data and diagnosis recorded at the hospitalization, as previously reported [13]. In order to protect privacy, information retrieved from the different databases were 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. Data analyses were performed by authorized staff only on remotely controlled computer. Any possibility to copy or export datasets was disabled. According to the rules from the Italian Medicines Agency (available at http://www.agenziafarmaco.gov.it/sites/default/files/det_20marzo2008.pdf), retrospective studies using administrative databases do not require Ethics Committee protocol approval.

3. Methodologies

3.1 Target dosages according to guidelines

In order to evaluate if the purchased drug quantity was in line with the expected target dosage, we considered an observation period of 365 days starting from the index date and we computed the total purchased milligrams of the main active principles for each pharmacological class of interest. Dividing these quantities by 365, we obtained the mean purchased daily doses (DD) of each active principle. Then, we divided them by the respective target dosages as recommended in the ESC Guidelines [4] or, for those drugs not included in the guidelines, as prescribed routinely in clinical practice and verified in the Italian Drug Agency's (in Italian: AIFA - Agenzia Italiana del Farmaco) website [14]. Thus, we obtained the standardized daily doses (sDD) that patients assumed during the observation period:

$$\text{sDD} = \frac{\text{mean purchased daily dose (DD) during observation period}}{\text{target dose recommended in ESC or AIFA guidelines}}.$$

If the sDD was 1, the mean purchased DD was equal to the target, whereas if it was $<$ or $>$ 1, it was less or higher than the target, respectively.

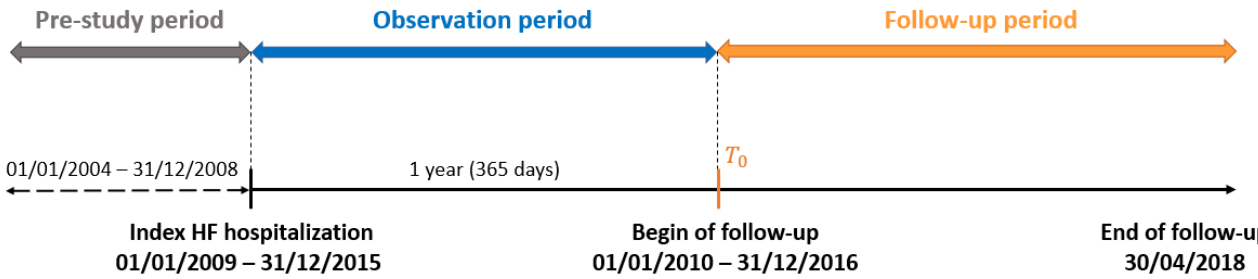

Figure 1. Study design.

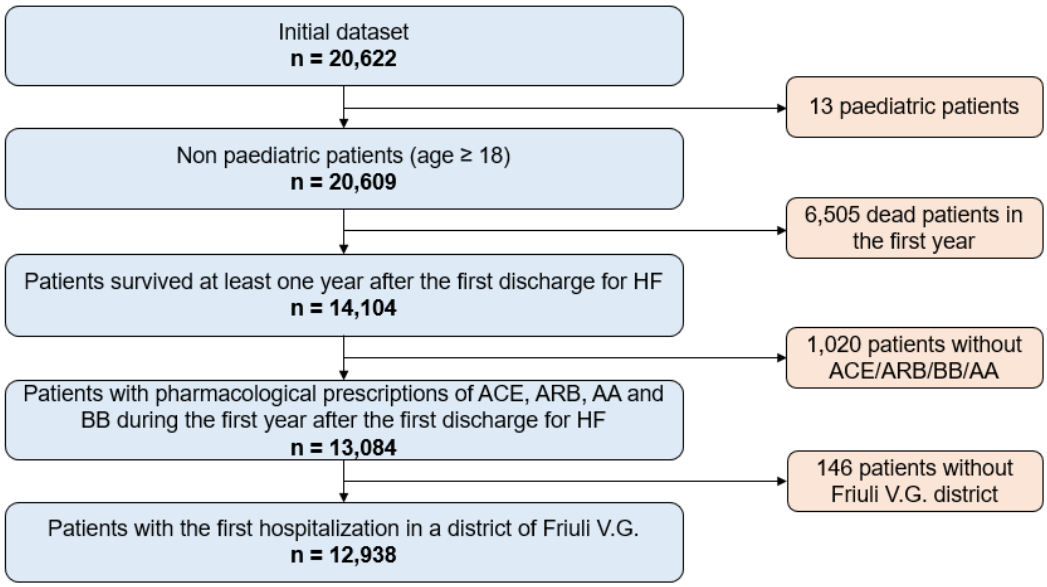

Figure 2. Flowchart of patient selection.
ACE = Angiotensin-Converting Enzyme inhibitors, ARB = Angiotensin Receptor Blockers, BB = Beta-Blocking agents, AA = Anti-Aldosterone agents

3.2 Adherence measures

In addition to evaluate the purchased drug quantity, we established if the drug was taken regularly during the observation period. According to [15,16] we calculated two measure of adherence, i.e. the Proportion of Days Covered (PDC), defined as:

$$PDC = \frac{\text{number of distinct coverage days}}{\text{number of days in the observation period}}$$

and the Medical Possession Ratio (MPR):

$$MPR = \frac{\text{number of days supplied during observation period}}{\text{number of days in the observation period}}$$

These measures were dichotomized to identify as adherent those patients with a PDC (or MPR) at least 80% [16]. For adherence computation of each of the disease-modifying pharmacological class (ACE/ARB, BB, AA) an observation period of 365 days from the index date was considered [15]. If during the observation period a patient was re-hospitalized or spent some time in ICU, we assumed that he/she was under treatment, i.e. he/she was taking all the purchased types of drug during those periods.

3.3 Adherence to polypharmacy

In order to evaluate polypharmacy, we introduced a new index, PAI (Patient Adherence Indicator), based on the ratio between the Poly-adherence (PA) and the Purchase Indicator (PI). These measures are computed using observed combinations of the three pharmacological classes of interest: BB, AA and ACE or ARB. PI is defined as the number of purchased types of drug at least once and it could be 1, 2 or 3 based on patient's different purchases. PA is the number of pharmacological classes to which the patient is adherent at the defined threshold of 80% (0, 1, 2 or 3):

$$PA = (\text{adherent to ACE or ARB}) + \text{adherent to BB} + \text{adherent to AA}$$

Finally, PAI is the number of pharmacological classes to which the patient is adherent divided by the number of purchased types of drug:

$$PAI = \frac{PA}{PI}$$

PAI considers poly-adherence and it could be 0, 1/3, 1/2, 2/3 or 1. Based on the overall PAI percentage, patients were divided into two groups: those with *poor* poly-adherence percentage (PAI $< 50\%$, i.e. $< 1/2$) and *good* poly-adherence percentage (PAI $\geq 50\%$, i.e. >=1/2).

3.4 Outcome measure

Study outcome of interest was patient's death for any cause. Deaths were collected from the Registry of Birth and Deaths included in the regional Data Warehouse. For the survival analysis, each patient was followed from one year after the index date (i.e. one year after the discharge from the index HF hospitalization) until the end of the study or the date of death (see follow-up period in *Figure 1*). The administrative censoring date was April 30th, 2018.

3.5 Survival Analysis: multivariable Cox regression models

In order to assess the role of PP adherence with respect to the overall survival time of a patient, we estimated four different Cox's regression models, one for each of the following PP indices: PAI and PAI group, computed with both PDC and MPR adherence measures. Each model was adjusted for nine covariates: WHF condition and discharge from CW at the index hospitalization, cardiological visit in the 24 months before the last hospitalization (i.e. the last hospitalization in the observation period), number of re-hospitalizations, number of ICU services and IHC activation during the observation period, Charlson index at the last hospitalization, age and gender at the beginning of the follow-up. The choice of these covariates was driven by clinical relevance and availability from administrative data. The hazard functions for each patient i were hence given by:

$$h_i\left(t \,|\, \boldsymbol{\omega}_i\right) = h_0(t)\exp\left\{\boldsymbol{\theta}^T \boldsymbol{\omega}_i\right\}$$

where the covariate vector for each patien was

$$\boldsymbol{\omega}_i = \left(\text{WHF}_i, \text{age}_i, \text{gender}_i, \text{charlson}_i, \text{CW}_i, \text{cardio}_i, \text{rehosp}_i, \text{ICU}_i, \text{IHC}_i, \omega_{10,i}\right)$$

with polypharmacy index $\omega_{10,i}$ equal to

$$\text{PAI\_PDC}_i \quad \text{or} \quad \text{PAI\_MPR}_i \quad \text{or} \quad \text{PAIgroup\_PDC}_i \quad \text{or} \quad \text{PAIgroup\_MPR}_i.$$

All the analyses were carried out using the free software R [17], in particular "survival" package [18,19]. Covariates with p-values < 0.05 were considered statistically significant.

4. Results

Patient characteristics are presented as numbers and percentages for categorical variables. For continuous variables we reported means with standard deviations or medians with interquartile ranges (IQRs), as appropriate depending on the distribution's shape.

4.1 Cohort selection

A total cohort of 20.622 patients were identified with principal diagnosis of HF. Of these, we excluded 13 paediatric patients. A substantial portion of patients (6505, 32%) was not considered because they died during the first year after the index hospitalization. Moreover, 1,020 patients (5%) were removed since they did not present any purchase of ACE, ARB, BB or AA during the observation period. Further, since their health residence district was not in FVG region, other 146 (0.7%) patients were excluded. Thus, a total of 12,938 (63%) patients met study selection criteria *(Figure 2)*.

Characteristics of study cohort are described in *Table 1* and *Table 2*. Overall, at index hospitalization (*Table 1*), mean age was 80 years with a substantial proportion of female patients (53.1%), high prevalence of De Novo patients (89.1%). Percentage of patients who have undergone at least one procedure was 4%. Comorbidity burden was high, with the median of Charlson index of 2 (46.8% with Charlson index ≥ 3). The rate of discharge from Cardiological Ward (CW) was 10.3%. In the 24 months before the index hospitalization, 6.030 (46.6%) patients underwent a cardiological visit.

Regarding pharmacological treatments, *Figure 3* shows percentages of purchase of medications at discharge according to monotherapy, bitherapy or tritherapy. In monotherapy the most common purchased drugs were BB (71%) and the less ones were ARB (27.1%, light-blue columns); moreover, ACE or ARB (ACE/ARB) was purchased by 83.2% of patients. Regarding PP, the most common drugs were ACE or ARB and BB (58.1%) and the less frequent were ARB and AA (11.5%, blue columns). Finally, the triplet ACE or ARB, BB and AA was purchased by 27.3% of patients (purple column).

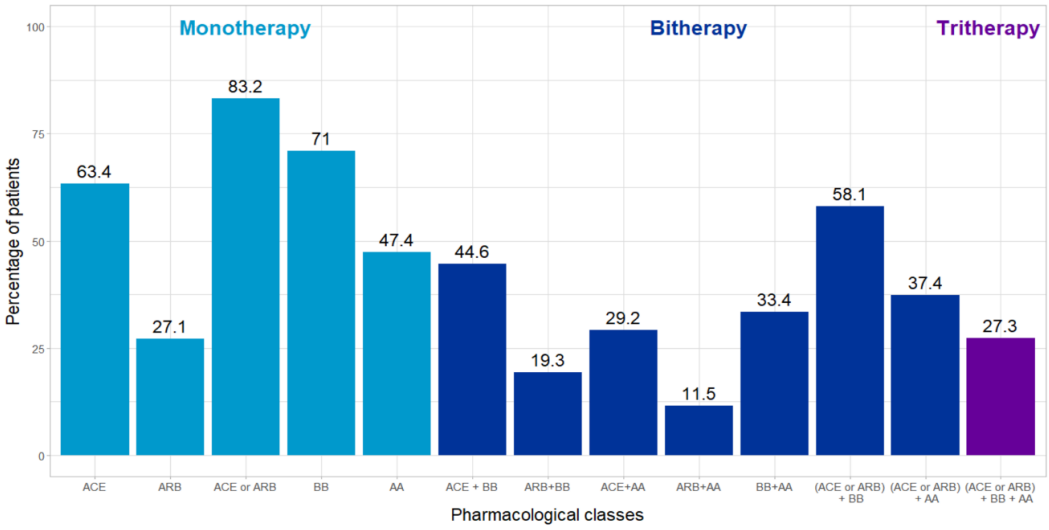

Figure 3. Barplots of percentages of patients in a monotherapy, a bitherapy or a tritherapy.

ACE = Angiotensin-Converting Enzyme inhibitors, ARB = Angiotensin Receptor Blockers, BB = Beta-Blocking agents, AA = Anti-Aldosterone agents.
'ACE or ARB' means that a patient presents at least one purchase for ACE and/or ARB during the observation period.
'ACE + BB' means that a patient presents at least one purchase both for ACE and for BB during the observation period.
ACE or ARB was considered as a unique class (ACE/ARB).
On the left, light-blue columns show percentages about monotherapy. Central blue columns show percentages about bitherapy. On the right, final purple column shows the percentage about tritherapy.

Table 1. Descriptive analysis of the whole cohort at index HF hospitalization.

Variable	**Study Cohort (12,938 pts)**	
Age at the first hospitalization	mean (s.d.)	79.77 (9.62)
Gender	*Female* (%) *Male* (%)	6,875 (53.1%) 6,063 (46.9%)
HF Condition	*De Novo* (%) *Worsening* (%)	11,531 (89.1%) 1,407 (10.9%)
Number of procedures*	0 (%) 1 (%) 2 (%) 3 (%) ≥ 4(%)	12,440 (96.1%) 411 (3.2%) 62 (0.5%) 25 (0.2%) 0 (0%)
Charlson index	median (Q1;Q3) < 3 ≥ 3	2 (1;4) 6,878 (53.2%) 6,060 (46.8%)
Cardiological Ward (CW)	0 (%) 1 (%)	11,602 (89.7%) 1,336 (10.3%)
Cardiological visit	0 (%) 1 (%)	6,908 (53.4%) 6,030 (46.6%)
Creatinine**	median (Q1;Q3) missing values (%)	1.09 (0.89;1.38) 1,599 (12.4%)
Glycated haemoglobin**	median (Q1;Q3) missing values (%)	6.6 (6.0;7.5) 10,084 (77.9%)
Haemoglobin**	median (Q1;Q3) missing values (%)	12.3 (11.0;13.6) 3,879 (30.0%)

ICU = Intermediate Care Unit, IHC = Integrated Home Care.

Cohort demographics for all patients. Age, gender, number of procedures, Charlson index, laboratory tests and discharge from CW refer to the first event, the index hospitalization. Cardiological visit refers to the 24 months before the index hospitalization. HF condition refers to the 5 years preceding the index admission.

* Examined procedures: Coronary Artery Bypass Graft surgery (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), implantation of drug-eluting stent in coronary artery, implanted cardioverter defibrillator, Cardiac Resynchronization Therapy (CRT), coronarography, pacemaker, Transcatheter Aortic Valve Implantation (TAVI) and MitraClip.

** Laboratory tests: median values (if available) of creatinine, glycated haemoglobin and haemoglobin measured during the index hospitalization. Creatinine and glycated haemoglobin values were integrated to hospital diagnosis in the Charlson index computation.

At the end of the observation period, i.e. one year after the index HF hospitalization, (*Table 2*), mean age was 81 years and the median of Charlson index remained high (47.4% with a Charlson index ≥ 3). Starting from the end of the observation period, during a median follow-up of 33 (IQR 17.1-55.1) months, 7.752 (59.9%) patients died. In the 24 months before the last hospitalization of the observation period, 6.786 (52.5%) patients underwent a cardiological visit. During the observation period, 53.6% patients were re-hospitalized at least once for any-cause, 13.7% for two times and 13.1% more than two times. In particular, 19.3% of patients were re-hospitalized at least once for HF. Moreover, 12.3% of patients admitted in ICU and IHC was activated at least once for 32.6% (4.220 pts) of the study cohort. Of note, for patients without any re-hospitalization during the observation period, the last hospitalization coincided with the index hospitalization.

Table 2. Descriptive analysis of the whole cohort at the beginning of follow-up period.

Variable	**Study Cohort (12,938 pts)**	
Age at the beginning of follow-up	mean (s.d.)	80.77 (9.62)
Follow-up time [months]	median (Q1;Q3)	33 (17.1;55.1)
Death	0 (%) 1 (%)	5,186 (40.1%) 7,752 (59.9%)
HF Condition of 7,752 patients who died during follow-up* **	*De Novo* (%) *Worsening* (%)	6,563 (84.7%) 1,189 (15.3%)
Charlson index*	median (Q1;Q3) < 3 ≥ 3	2 (1;4) 6,801 (52.6%) 6,137 (47.4%)
Cardiological visit**	0 (%) 1 (%)	6,152 (47.5%) 6,786 (52.5%)
Number of all-cause re-Hospitalizations	0 (%) 1 (%) 2 (%) ≥ 3 (%)	6,006 (46.4%) 3,462 (26.8%) 1,775 (13.7%) 1,695 (13.1%)
Number of HF re-Hospitalizations	0 (%) 1 (%) 2 (%) ≥ 3 (%)	10,422 (80.7%) 1,896 (14.7%) 437 (3.4%) 163 (1.2%)
Number of ICU services	0 (%) 1 (%) ≥ 2 (%)	11,356 (87.7%) 1,305 (10.1%) 277 (2.2%)
IHC activation	0 (%) 1 (%)	8,718 (67.4%) 4,220 (32.6%)

ICU = Intermediate Care Unit, IHC = Integrated Home Care.
Cohort demographics for all patients. Age and gender refer to the end of the observation period (one year after the index hospitalization). Charlson index refers to the last hospitalization during the observation period. Cardiological visit refers to the 24 months before the last hospitalization. Number of re-hospitalizations, number of ICU and IHC activation refer to the observation period (365 days starting from the first discharge for HF).
* Wilcoxon tests with respect index date: alternative = "two sides" p-value = 3.187e-05 - alternative = "less" p-value = 1
** McNemar test on proportions with respect index date: p-value = < 2e-16
*** Chi-square p value < 0.0001

4.2 Standardized daily dose

Figure 4 shows the standardized daily dose of each pharmacological treatment.

For ACE, medians of standardized daily doses were 29% of the target dosage (IQR 15%-50%) for ramipril, 38% (IQR 15%-88%) for enalapril and 46% (IQR 21%-92%) for lisinopril. Percentages of patients with doses > 100% of target dosage were 4.1%, 15.3% and 13.8%, for ramipril, enalapril and lisinopril, respectively.

For ARB, medians of standardized daily doses were 31% (IQR 15%-38%) for losartan, 25% (IQR 12%-50%) for valsartan, 31% (IQR 15%-54%) for olmesartan, 46% (IQR 23%-92%) for telmisartan and 25% (IQR

12%-46%) for candesartan. Percentages of patients with doses > 100% of target dosage were 0.2%, 3.2%, 4.7%, 14.3% and 2.8%, for losartan, valsartan, olmesartan, telmisartan and candesartan, respectively.

For AA, medians of standardized daily doses were 34% (IQR 13%-47%) for spironolactone, 66% (IQR 33%-121%) for potassium canrenoate and 55% (IQR 22%-88%) for canrenone. Percentages of patients with doses > 100% of target dosage were 2.9%, 32.1% and 17.8%, for spironolactone, potassium canrenoate and canrenone, respectively.

Finally, for BB, medians of standardized daily doses were 19% (IQR 12%-31%) for bisoprolol, 26% (IQR 13%-50%) for carvedilol, 41% (IQR 21%-58%) for metoprolol and 31% (IQR 15%-46%) for nebivolol. Percentages of patients with doses > 100% of target dosage were 1.5%, 2.7%, 3.5% and 0.6%, for bisoprolol, carvedilol, metoprolol and nebivolol, respectively.

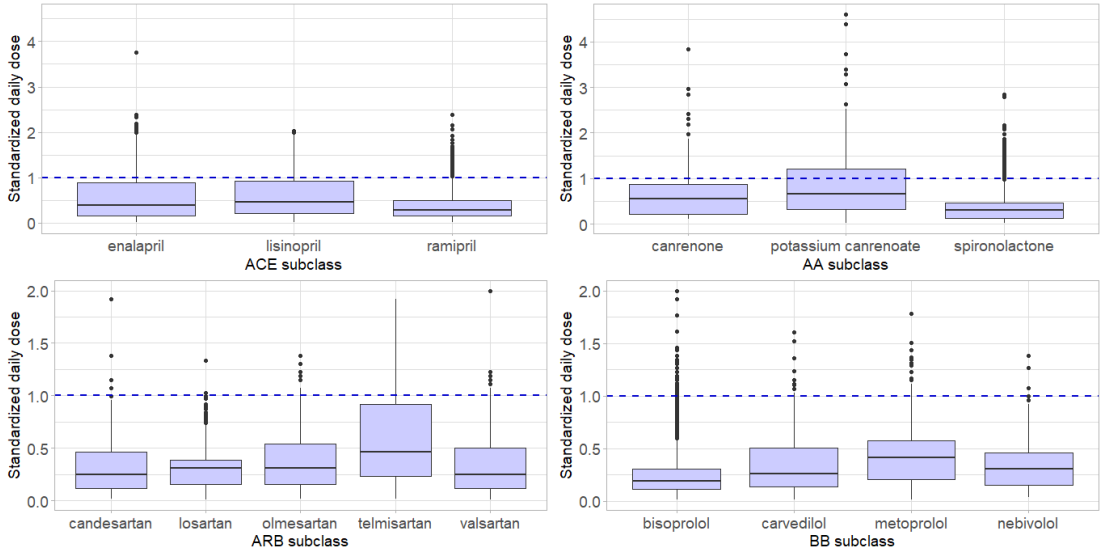

Figure 4. Boxplots of standardized daily dose (sDD) for the main active principles of each pharmacological class.

ACE = Angiotensin-Converting Enzyme inhibitors, ARB = Angiotensin Receptor Blockers, BB = Beta-Blocking agents, AA = Anti-Aldosterone agents.

Top-left panel reports ACE main subclasses: enalapril, lisinopril and ramipril.

Top-right panel reports AA main subclasses: canrenone, potassium canrenoate and spironolactone.

Down-left panel reports ARB main subclasses: candesartan, losartan, olmesartan, telmisartan and valsartan.

Down-right panel report BB main subclasses: bisoprolol, carvedilol, metoprolol and nebivolol.

Dashed blue lines (standardized daily dose = 1) indicate that the mean purchased DD are equal to the respective target dosages recommended in the ESC Guidelines [4] or according to clinical practice of AIFA's website [14].

Table 3. Descriptive analysis of Patient Adherence Indicators (PAIs) of the whole cohort.

PP Index	PP scale	PDC	MPR
PAI	0 (%)	6,107 (47.2%)	3,758 (29.1%)
	1/3 (%)	1,438 (11.1%)	1,480 (11.4%)
	1/2 (%)	2,653 (20.5%)	3,080 (23.8%)
	2/3 (%)	654 (5.1%)	1,139 (8.8%)
	1 (%)	2,086 (16.1%)	3,481 (26.9%)
PAI group	*good* (%)	5,393 (41.7%)	7,700 (59.5%)
	poor (%)	7,545 (58.3%)	5,238 (40.5%)

PDC = Proportion of Days Covered, MPR = Medical Possession Ratio, as explained in section Adherence measures. PAI = Patient Adherence Indicator, as explained in section Polypharmacy indices. PDC column refers to PAI computed with PDC adherence results. MPR column refers to PAI computed with MPR adherence results.

4.3 Patients' adherence measures

Using PDC, at the end of the observation period 47.2% of 8.199 ACE patients, 39.7% of 3.503 ARB patients, 22.6% of 9.183 BB patients, 18.3% of 6.137 AA patients and 48.5% of 10.759 of ACE or ARB patients were adherent to the corresponding treatment at the threshold of 80%.

Using MPR measure, percentages were higher: 63% of ACE patients, 58.5% of ARB patients, 36% of BB patients, 31.5% of AA patients and 66% of ACE or ARB patients. Descriptive statistics about PP indices of the study cohort are reported in *Table 3*.

Using PDC, the following PAI values emerged: 47.2% (0, n = 6.107), 11.1% (1/3, n=1.438), 20.5% (1/2, n=2.653), 5.1% (2/3, n=654) and 16.1% (1, n = 2.086). Consequently, 41.7% of the patients had good poly-adherence percentage (n = 5.393). Using MPR, the following PAI values were calculated: 29.1% (0, n = 3.758), 11.4% (1/3, n = 1.480), 23.8% (1/2, n = 3.080), 8.8% (2/3, n = 1.139) and 26.9% (1, n = 3.481). Consequently, 59.5% of the patients had good poly-adherence percentage (n = 7.700).

4.4 Multivariable Cox models for survival outcome

In *Table 4* impact of covariates on survival for each Cox model is displayed. In particular, in all models the risk of death was increased in WHF patients, elderly, males, high Charlson index, number of re-hospitalizations, ICU and IHC admission during the observation period. Conversely, a protective role of discharge from a cardiological ward (CW) and of a previous cardiological visit was observed. Regarding PP indices, both PAI (first and second model) and PAI group (third and fourth models) were significantly protective (HRs < 1). In particular, the risk of death decreased with higher values of PAI, as expected, and patients with *good* poly-adherence percentage presented a lower risk of mortality. *Figure 5* shows this result through the estimate of survival stratified by *good* and *poor* levels in the case of PAI group computed using MPR (fourth model).

To estimate survival curves, categories were selected according to the following criteria: we considered a female-De Novo patient aged 82 years old with a previous cardiological visit and a Charlson index at the last hospitalization equal to 2. Moreover, at index HF hospitalization this patient was not discharged from CW and during the observation period she was re-hospitalized only once and did not benefit of any ICU service or IHC activation.

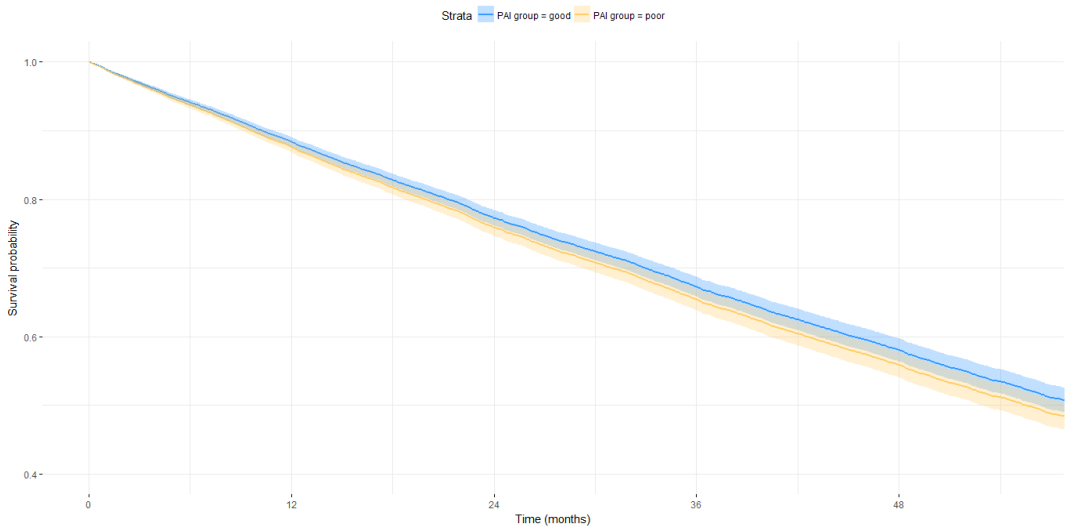

Figure 5. Estimated survival from the Cox model stratified by *good* and *poor* patients in the case of PAI group computed using MPR.

Table 4. Adjusted Hazard Ratios with 95% Confidence Intervals (CI) and p-values of each Cox's model.

	Model 1 - PDC		Model 2 - MPR	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
HF Condition (WHF)	1.24 (1.16-1.32)	6.77e-11	1.24 (1.16-1.32)	7.33e-11
Age	1.06 (1.06-1.07)	< 2e-16	1.06 (1.06-1.07)	< 2e-16
Gender (M)	1.32 (1.26-1.39)	< 2e-16	1.32 (1.26-1.39)	< 2e-16
Charlson index	1.11 (1.09-1.12)	< 2e-16	1.11 (1.09-1.12)	< 2e-16
CW (1)	0.78 (0.71-0.85)	1.97e-07	0.78 (0.71-0.86)	2.39e-07
Cardio visit (1)	0.94 (0.89-0.98)	0.00439	0.94 (0.90-0.98)	0.00563
Re-hospitalizations	1.11 (1.10-1.13)	< 2e-16	1.12 (1.10-1.13)	< 2e-16
ICU services	1.14 (1.09-1.20)	4.18e-08	1.14 (1.09-1.20)	3.12e-08
IHC activation (1)	1.27 (1.22-1.34)	< 2e-16	1.28 (1.22-1.34)	< 2e-16
PAI	0.91 (0.85-0.97)	0.00270	0.94 (0.89-0.99)	0.03819
	Model 3 - PDC		**Model 4 - MPR**	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
HF Condition (WHF)	1.24 (1.16-1.32)	9.33e-11	1.24 (1.16-1.32)	7.97e-11
Age	1.06 (1.06-1.07)	< 2e-16	1.06 (1.06-1.07)	< 2e-16
Gender (M)	1.32 (1.26-1.39)	< 2e-16	1.32 (1.26-1.39)	< 2e-16
Charlson index	1.11 (1.09-1.12)	< 2e-16	1.11 (1.09-1.12)	< 2e-16
CW (1)	0.78 (0.71-0.85)	1.63e-07	0.78 (0.71-0.85)	1.89e-07
Cardio visit (1)	0.94 (0.89-0.98)	0.00466	0.94 (0.90-0.98)	0.00572
Re-hospitalizations	1.11 (1.10-1.13)	< 2e-16	1.11 (1.10-1.13)	< 2e-16
ICU services	1.14 (1.09-1.20)	3.73e-08	1.14 (1.09-1.20)	3.20e-08
IHC activation (1)	1.27 (1.22-1.34)	< 2e-16	1.28 (1.22-1.34)	< 2e-16
PAI group (good)	0.93 (0.88-0.97)	0.00119	0.93 (0.89-0.98)	0.00354

PDC = Proportion of Days Covered, MPR = Medical Possession Ratio, as explained in section Adherence measures.
CW= Cardiological Ward, ICU = Intermediate Care Unit, IHC = Integrated Home Care.
PAI = Patient Adherence Indicator, as explained in section Polypharmacy indices.
PDC columns refer to PAI/PAI group computed with PDC adherence results. MPR columns refers to PAI/PAI group computed with MPR adherence results.
Each column corresponds to a different Cox's regression models, one for each of the following PP indices: PAI and PAI group computed with both PDC and MPR adherence results.
Each model was adjusted for nine time-independent covariates: HF condition and discharge from CW at index hospitalization, cardiological visit in the 24 months before the last hospitalization, number of re-hospitalizations, number of ICU services and IHC activation during the observation period, Charlson index at the last hospitalization, age and gender at the beginning of the follow-up period.

5. Discussion

Our current analysis showed that (i) patients' adherence to disease modifying-treatment was satisfactory in terms of percentages; (ii) integration of dosages of these medications and polypharmacy into the adherence assessment reduced significantly the proportion of patients with good adherence; (iii) a similar trend in reduction of adherence was observed when we considered polypharmacy adherence, based on the new proposed index of PAI; (iv) a good poly-adherence for the prescribed drugs among ACE or ARB, BB, AA during one year after an episode of HF hospitalization was associated with improved survival irrespective from the specific measure of adherence used (MPR or PDC).

To date, few data exist regarding the adherence of drug therapies in a real world setting for HF patients. Indeed, most of previous data have been focused on applications of recommended medications in HF patients [10, 20] but no data are available on drug's purchases, thus limiting our knowledge of the patients' adherence in HF setting. For the first time, we performed an analysis on patients adherence by considering purchases and adherence patterns. In this sense, our study extend and reinforce previous results. Specifically, our analysis showed that patients' adherence to oral treatment of HF medications was satisfactory. This is in line with previous observations that have underlined that adherence to HF guidelines regarding prescriptions of appropriate classes of therapy has improved considerably over the past decade from approximately a quarter of prescriptions in 2008 to nearly two thirds in 2016 [11]. However, even when prescriptions of guideline-based HF treatment is high, there is evidence of frequent failures to reach target doses [20]. In this respect, our study confirmed that high proportion of HF patients received an under-dosing of recommended therapies. Data from quality surveys reported similar trend in the prescriptions, with less than one-third of patients on guideline-recommended target dosages [10]. Similarly, a recent European survey (BIOSTAT-CHF) conducted in 11 countries and enrolling 2500 patients showed that only a minority of patients reached the target dose of ACEI and BB [21]. These trends confirmed that simple calculation of the percentage of "treated" patients may not be an adequate measure to indicate the quality of healthcare provided for HF patients, and that under-dosing of recommended therapies remain a major issue. Worth of note, we focused on patient's adherence in 1-year from an HF hospitalization. In this observation period, we found that treatment with oral BB, ACE/ARB and AA were present in one-third of patients, and this trend was lower when we considered target dosages.

The two methods of adherence calculations - based on PDC and MPR- showed differences in terms of percentages of adherent patients estimated for the specific drugs classes. These differences may be due to the fact that adherence could be underestimated by measures which ignore overlaps (i.e. PDC) and overestimated by ones which count overlaps (i.e. MPR) during the observation period. In the current literature, PDC is the suggested method to reflect adherence behaviour of patients who are prescribed multiple medications concurrently within a class [22]. No relevant prognostic differences were present when PDC or MPR-based measures were combined in the PAI index, even though PDC and MPR showed different percentages on single drug classes. This could indicate that adherence to drugs combinations is prognostically more relevant, irrespective from the measure adopted.Perhaps more notably, PAI measures for estimating patient's polypharmacy adherence indicated that patients with co-treatments with three-class drugs showed very low values of adherence with 11.4% of patients assuming 1/3 and 8.8% assuming 2/3.

Our study indicated that the risk of death significantly decreased with a good poly-adherence percentage. Importantly, we reported poly-adherence measures on effective purchases exploiting the potential of administrative health care databases. The proposed index PAI can be viewed as a modified version of the Guideline Adherence Indicator, GAI, [9] that was based on medical prescriptions at discharge and not on effective patient's purchases and adherence patterns. The significant PAI effect on survival suggests that medication nonadherence is associated with lower survival probability also in the case of PP therapy, so extending previous results about the effect of nonadherence to specific drugs classes [21].

Some limitations of the present study have to be noted: first, no clinical data were available about New York Heart Association (NYHA) class or Left Ventricular Ejection Fraction (LVEF), therefore it was not possible to evaluate a stratification of the patients according to clinical HF severity; as a proxy, we used previous HF hospitalization in the patient history. Second, in the PDC and MPR computations, theoretical Defined Daily Doses (DDD), available from administrative health data were used instead of Prescribed Daily Doses (PDD) and therefore a bias could be present in the estimated adherence if the underlying PDD:DDD ratio is different from 1 [23, 24]. Third, the cut-off of PDC or MPR greater than 80% to define patient adherence could be further examined in a sensitivity analysis in order to find if other values or a distribution of thresholds could better stratify patient's outcome. Finally, some technical improvements may be included into the PAI definition in order to provide a more elaborated formula which is able to reward more patients that are adherent in PP with respect to those adherent in monotherapy. In the present definition of PAI a patient scores 1 if he/she is fully adherent to only one drug or if he/she is fully adherent to a combination of drugs. For example, the PAI definition could be modified combining the terms with some weights, in order to maximize the predictive capacity of the model and producing a more refined grading score among patients. This aspect will be explored in future work. Finally, since we excluded from the study cohort patients not surviving the first year of follow up, alternative statistical approaches that models PP adherence a as a time-dependent covariate, in order to avoid this selection, could be explored in future applications.

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