ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 1944–1953
Published online 4 March 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13223

ORIGINAL RESEARCH ARTICLE

Adherence and optimization of angiotensin converting enzyme inhibitor/angiotensin II receptors blockers and beta-blockers in patients hospitalized for acute heart failure

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Abstract

Aims Treatment with angiotensin converting enzyme inhibitor (ACEi)/angiotensin II receptors blockers (ARBs) and beta-blockers is frequently suboptimal at discharge in patients hospitalized for acute heart failure (AHF). We investigated the prognostic significance of medical treatment at discharge and its changes during hospitalization.

Methods and results In a retrospective analysis, we included 623 patients hospitalized for AHF with reduced left ventricular ejection fraction (<40%). The primary endpoint was all-cause mortality and heart failure rehospitalization to Day 180 since hospital discharge. A total of 249 (42.4%) of patients received no ACEi/ARBs/BB or <50% target dose (TD) of these drugs, 249 (42.4%) had either ACEi/ARBs or BB ≥ 50% of TD, and 89 (15.2%) ACEi/ARBs and BB ≥ 50% of TD at discharge. The primary endpoint was significantly lower in patients receiving at least one drug ≥50% of TD compared with no or low-dose treatment (ACEi/ARBs or BB ≥ 50% TD: adjusted hazard ratio (HR) 0.69, 95% confidence interval (CI) [0.49–0.98], $P = 0.04$; ACEi/ARBs and BB ≥ 50% TD: adjusted HR 0.54, 95% CI [0.30–0.96], $P = 0.03$). With regard to treatment changes from admission to discharge, therapy was decreased in 258 (44.6%) patients, stable in 194 (33.6%), and increased in 126 (21.8%). Compared with patients with stable therapy, treatment intensification was associated with a lower rate of the primary endpoint (adjusted HR 0.49, 95% CI [0.29–0.83]; $P = 0.01$).

Conclusions In patients with AHF, prescription of ACEi/ARBs/BB ≥ 50% TD at the time of discharge, whether achieved or not through treatment intensification during the hospitalization, is associated with better post-discharge outcomes.

Keywords Acute heart failure; ACE-inhibitors; Beta-blockers; Therapy; Outcomes

Received: 13 August 2020; Revised: 17 December 2020; Accepted: 7 January 2021
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Introduction

International guidelines strongly recommend the implementation of angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptors blockers (ARBs), and beta-blockers (BBs) in stable patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF) to improve outcomes.[1] However, in the real world, the prescription of such therapies is still suboptimal in a large proportion of patients.[2] The benefits of ACEi/ARBs and BB are well established in chronic HF; however, few evidences are still available for acute patients, and in the European Guidelines, the implementation of such therapies at discharge, despite being strongly recommended, has a low level of evidence (class of recommendation I, level of evidence C).[1]

In patients discharged after acute HF (AHF), hypotension and worsening renal function may further prevent the introduction and intensification of oral therapies if not resulting in decrease or withdrawal.[3–6] Recently, some studies showed that in AHF patients treatment at discharge with ACEi/ARBs and BB is associated with improved outcomes.[4,7,8] Data from the large GREAT registry showed that the use of either or both ACEi/ARBs and BB is associated with a significant reduction of 90 day and 1 year all-cause mortality.[4] This has important implications because optimal medical treatment could at least improve outcomes in the vulnerable phase after discharge which is characterized by high mortality and rehospitalization rates.[1,9–12]

Current information regarding treatment optimization after AHF discharge is mostly qualitative, focusing on the prescription or not of ACEi/ARBs and BB and without including data related to the prescribed dose, which may not be available in registries. Notably, even if the prescription rates of ACEi/ARBs and BB increased in the last years, the proportion of patients receiving optimal treatment is still low.[1,13] In addition, recent studies showed that only a high-intensity treatment with at least the 50% of the target dose (TD) is actually effective in improving prognosis with similar outcomes whether the patients achieve just >50% or up to 100% TDs.[14,15]

Another aspect that needs to be better explored is the impact of oral therapies changes during the hospitalization. Even if there is a large consensus regarding the need to maintain oral therapies and the discontinuation of BBs has been associated with untoward outcomes,[16–18] it is still unclear if an early treatment intensification before discharge could be beneficial in terms of mortality and rehospitalization rates.

The aims of this study are to evaluate the prescription of ACEi/ARBs and BB at discharge in patients hospitalized for AHF and to assess the prognostic significance of optimal treatment at discharge and of treatment changes between admission and discharge.

Methods

Study population

In this study, we included a retrospective cohort of 1021 patients hospitalized for AHF from 2003 to 2019 at the Cardiology Department of *Spedali Civili* of Brescia, Italy. The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the local institutional board.

Inclusion criteria were signs and symptoms of AHF with the need of intravenous diuretic treatment and New York Heart Association Class III/IV at admission. Patients with the following characteristics were excluded: evidence of acute coronary syndrome at admission; cardiogenic shock and/or signs of hypoperfusion; HF due to significant arrhythmias; myocarditis at admission; valvular heart disease (including moderate to severe aortic or mitral valve stenosis, severe aortic regurgitation, and severe primary mitral regurgitation); cardiac tamponade; aortic dissection; restrictive, hypertrophic or systemic illness-related cardiomyopathy; dyspnoea due to non-cardiovascular causes.

Medical history was recorded at admission. All patients underwent complete physical examination at admission and discharge. The presence of congestion was evaluated as a score based on the presence of peripheral oedema, pulmonary rales, and jugular vein distension. Laboratory tests were performed at admission and at discharge. N terminal prohormone brain natriuretic peptide (NT-proBNP) was measured at discharge using Elecsys assay (Roche Diagnostics, Inc., Monza–Milan, Italy). Estimated glomerular filtration rate was calculated with the simplified Modification of Diet in Renal Disease equation based on serum creatinine value.

Echocardiography was performed during hospitalization and LVEF was calculated using the biplane Simpson method according the international guidelines.[19]

Data regarding follow-up were collected from hospital records, telephone contact with the patient, a family member, or with the general practitioner. The follow-up duration was from discharge to Day 180. The primary endpoint was the composite all-cause death and HF rehospitalization by Day 180, whichever occurred first. The secondary endpoints were all-cause death by Day 180 and HF rehospitalization by Day 180. Outcomes adjudication was performed by two independent investigators (V. C. and T. D.); in case of discordance, the case was discussed within our study staff.

Pharmacological therapy

Pharmacological treatment was evaluated at admission and discharge, as use of an ACEi or ARB, and of a BB. Percentages of the TD were calculated on the basis of current European Society of Cardiology guidelines, and molecules not approved for the treatment of HF and reduced LVEF were not considered for each specific analysis.[1]

The diuretic dose was expressed as furosemide dose or equivalent and was collected at admission (as home therapy), as cumulative intravenous diuretic dose during the first 24 h from admission, and at discharge. We also recorded the proportion of patients treated with intravenous nitrates and inotropes during hospital stay.

For the purposes of this study, we first categorized the percentages of TD, ACEi/ARBs, and BB, respectively, into three strata of increasing adherence to guidelines as follows: no prescription, <50% TD, or ≥50% TD. For each patient, moreover, the combination of ACEi/ARBs and BB was categorized into groups of increasing adherence as follows: (i) no

ACEi/ARB/BB or <50% TD, (ii) ACEi/ARBs *or* BB ≥ 50% TD, and (iii) ACEi/ARBs *and* BB ≥ 50% TD.

Statistical analysis

We divided our study population into groups on the basis of the percentage of TD of ACEi/ARBs and/or BB at admission and at discharge and investigated their role as predictors of the combined primary endpoint of all-cause death and HF re-hospitalization to Day 180.

We performed two analyses for the combined treatment: in the first one, we considered the percentage of TD at discharge categorized in the three increasing adherence groups described in the previous paragraph, while in the second one, we evaluated changes from admission to discharge dividing patients into three groups as follows: (i) decreased dose (including no ACEi/ARB/BB or <50% TD at both admission and discharge), stable dose (same percentage of TD group, with the exclusion of no ACEi/ARB/BB or <50% TD at both admission and discharge), and increased dose.

We also investigated the independent association of either ACEi/ARBs or BB, at discharge (as no prescription, <50% TD, or ≥50% TD) or as changes from admission to discharge (as decreased dose or no prescription, stable dose excluding no prescription, or increased percentage of TD). These and other potential predictors of the primary endpoint were investigated at univariate analysis: continuous variables were shown as means and standard deviations, skewed variables as medians and interquartile ranges, dichotomous variables as counts and percentages; comparisons were made, respectively, using *t* test for means, Wilcoxon test for medians, and χ^{12} test for proportions.

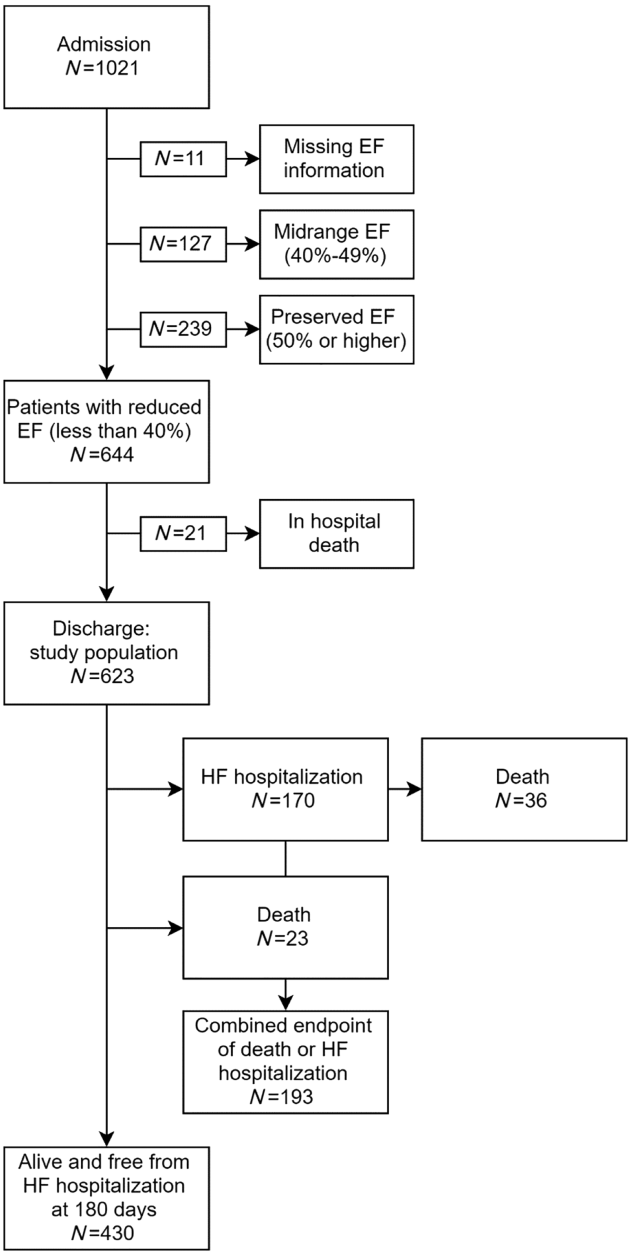
Time to combined event during the 180 days follow-up was defined as the time from discharge to the combined event occurrence (the date of death or the date of HF rehospitalization was considered in the time to event analysis). Patients that were free of events at the end of the 180 days follow-up were censored at that time. HF hospitalization-free survival to Day 180 was analysed by Kaplan–Meier method, and differences between strata were investigated by the log-rank test. Univariable and multivariable Cox regression models were implemented using therapy (in combination or alone) at discharge or its variation as main predictor and adjusting for clinically relevant confounders as age, sex, chronic obstructive pulmonary disease, ischaemic cardiomyopathy, body mass index, systolic blood pressure, haemoglobin, and estimated glomerular filtration rate. The hazard ratios (HRs), 95% confidence intervals (CIs) and *P* values from a Wald test were calculated.

A two-tailed *P* value <0.05 was considered statistically significant. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Of a total of 1021 patients hospitalized for AHF, we excluded 377 patients with LVEF ≥ 40% (*N* = 366) or missing information on LVEF (*N* = 11). Twenty-one patients were excluded for in-hospital death resulting in a study population of 623 patients (*Figure 1*).

Figure 1 Flow diagram of the study population.



Therapy with angiotensin converting enzyme inhibitor/angiotensin II receptors blockers and beta-blockers at discharge

Three hundred and eighty-five (61.8%) patients were prescribed ACEi at discharge, 120 (19.3%) patients ARBs, for a total of 480 (77.0%) patients on ACEi/ARBs. BBs were administered in 525 (84.3%) patients at discharge (*Table S1*). The proportions of patients who were treated with ≥50% of TD were 40.8% for ACEi/ARBs and 31.6% for BB (*Table 1*). A total of 249 (42.4%) of patients were classified as no ACEi/ARBs/BB or <50% of TD, 249 (42.4%) as ACEi/ARBs or BB ≥ 50% of TD, and 89 (15.2%) as ACEi/ARBs and BB ≥ 50% of TD.

Clinical characteristics at discharge of the study population are listed in *Table 2*. The group of patients treated with ACEi/ARBs and BB ≥ 50% of TD at discharge showed a younger age, a higher prevalence of male sex, and a lower proportion of ischaemic cardiomyopathy compared with groups with lower level of prescription. Patients who received optimal medical therapy at discharge had higher body mass index, less comorbidities, and lower signs and symptoms of congestion as well as lower NT-proBNP values at discharge, compared with other groups. Renal function was better in patients on optimal treatment and progressively worsened in patients on either ACEi/ARBs or BB ≥ 50% of TD and in patients with <50% of TD or no therapy at discharge. The median dose of intravenous furosemide given during the first 24 h from admission was lower in patients receiving optimal dose of both ACEi/ARBs and BB compared with other groups.

Patients were followed for a median follow-up time of 180 days after discharge. Overall, 59 (9.5%) patients died, 170 (27.3%) were rehospitalized for HF, and 193 (31.0%) had the combined primary endpoints. Treatment with both ACEi/ARBs or BB ≥ 50% of TD and with ACEi/ARBs and BB ≥ 50% of TD were associated with a significant lower rate of the primary endpoint compared with patients with no or low-dose treatment (log-rank *P* value <0.001 and 0.01, respectively) whereas no significant differences were observed between the groups of patients receiving at least one drug ≥50% of TD (log-rank *P* value 0.10). (*Table 4*, *Figure 2*).

Considering treatment at discharge, Cox regression analysis for the primary endpoint to Day 180 showed that treatment with ACEi/ARBs or/and BB ≥ 50% TD were independent predictors of better outcomes in comparison with no or low-dose treatment group (ACEi/ARBs or BB ≥ 50% TD: adjusted HR 0.69, 95% CI [0.49–0.98], *P* = 0.04; ACEi/ARBs and BB ≥ 50% TD: adjusted HR 0.54, 95% CI [0.30–0.96], *P* = 0.03). The use of ACEi/ARBs ≥50% of TD was independently associated with improved prognosis, while the use of BB at ≥50% TD was not significant after adjustment for relevant confounders (*Table 5*).

Table 1 Therapy with ACEi/ARBs and BBs at discharge and variation from admission to discharge (*N* = 623)

	N with data	*N* (%)
Therapy at discharge	587	
No ACEi/ARBs/BB or <50%TD		249 (42.4)
ACEi/ARBs or BB ≥ 50% of TD		249 (42.4)
ACEi/ARBs and BB ≥ 50% of TD		89 (15.2)
ACEi/ARBs at discharge	595	
No		143 (24.0)
<50% TD		209 (35.1)
≥50% TD		243 (40.8)
BB at discharge	614	
No		89 (14.5)
<50% TD		331 (53.9)
≥50% TD		194 (31.6)
Therapy variation from admission to discharge	578	
Decreased		258 (44.6)
Stable		194 (33.6)
Increased		126 (21.8)
ACEi/ARBs variation	593	
Decreased		208 (35.1)
Stable		215 (36.3)
Increased		170 (28.7)
BB variation	606	
Decreased		127 (21.0)
Stable		181 (29.9)
Increased		298 (49.2)

ACEi, angiotensin converting enzyme inhibitor; ARBs, angiotensin II receptors blocker; BBs, beta-blockers; TD, target dose.
Data shown as count (%).

Changes in therapy with angiotensin converting enzyme inhibitor/angiotensin II receptors blockers and beta-blocker from admission to discharge

Of a total of 578 patients with available data, therapy was decreased from admission to discharge in 258 (44.6%) of patients, stable in 194 (33.6%), and increased in 126 (21.8%) (*Table 1*). Considering individual changes of ACEi/ARBs and BB, the proportion of patients who underwent treatment intensification were 28.7% and 49.2%, respectively (*Table 1*, *Figure* S1). Clinical characteristics according to therapy change from admission to discharge are reported in *Table 3*. Patients with treatment increase were younger, with less comorbidities (with the exception of arterial hypertension) and had less frequently an ischaemic cardiomyopathy. They had also less sign and symptoms of congestion, lower NT-proBNP, and better renal function compared with patients with reduced treatment. Female sex was more represented in the subgroup of patients with therapy reduction. No significant differences in vital signs were observed across groups.

The primary endpoint was significantly lower in patients who intensified treatment in comparison with patients with decreased (log-rank *P* value <0.001) and stable therapy

Table 2 Patients characteristics according to therapy at discharge (N = 587 with non-missing information)

	No ACEi/ARBs/BB or <50%TD N = 249	ACEi/ARBs or BB ≥ 50% of TD N = 249	ACEi/ARBs and BB ≥ 50% of TD N = 89	P
General characteristics				
Age, years	71.2 ± 11.6	68.0 ± 10.7	62.9 ± 10.5	<0.001
Sex, male	193 (77.5)	222 (89.2)	85 (95.5)	<0.001
BMI (kg/m^2)	24.5 ± 4.2	25.8 ± 4.7	26.9 ± 5.9	<0.001
NYHA Class III/IV	74 (29.7)	52 (20.9)	14 (15.7)	0.01
Congestion score ≥2[a]	40 (16.1)	28 (11.2)	6 (6.7)	0.05
SBP (mmHg)	109.3 ± 16.0	111.9 ± 17.5	113.4 ± 15.4	0.08
HR (bpm)	70.1 ± 11.0	68.1 ± 10.6	67.6 ± 9.5	0.05
LVEF (%)	25.9 ± 6.9	26.0 ± 7.1	25.4 ± 7.2	0.80
ICD	94 (37.8)	86 (34.5)	42 (47.2)	0.11
CRT	71 (28.5)	50 (20.1)	26 (29.2)	0.06
HF aetiology				
Non-ischaemic dilated cardiomyopathy (%)	103 (41.4)	97 (39.0)	44 (49.4)	0.06
Ischaemic cardiomyopathy (%)	141 (56.6)	145 (58.2)	39 (43.8)	
Hypertensive cardiomyopathy (%)	5 (2.0)	7 (2.8)	6 (6.7)	
Medical history				
Previous HF	182 (73.1)	194 (77.9)	69 (77.5)	0.42
Diabetes mellitus	70 (28.1)	96 (38.6)	26 (29.2)	0.03
Arterial hypertension	114 (45.8)	149 (59.8)	53 (59.6)	0.004
Atrial fibrillation	102 (41.0)	99 (39.8)	36 (40.4)	0.96
COPD	62 (24.9)	50 (20.1)	10 (11.2)	0.02
CKD	126 (50.6)	91 (36.5)	29 (32.6)	0.001
Laboratory				
Hb (g/dL)	12.4 ± 1.8	12.7 ± 1.8	13.5 ± 1.8	<0.001
Serum creatinine (mg/dL)	1.5 (1.2–2.1)	1.4 (1.1–1.8)	1.3 (1.0–1.7)	<0.001
eGFR (mL/min/1.73 m^2)	44.1 (30.5–59.6)	52.2 (38.5–73.5)	60.1 (43.7–83.4)	<0.001
Sodium (mEq/L)	139.1 ± 4.4	139.0 ± 4.0	139.7 ± 3.5	0.39
Bilirubin (mg/dL)	0.77 (0.56–1.10)	0.80 (0.58–1.04)	0.80 (0.52–1.01)	0.76
AST (U/L)	24 (18–34)	23 (19–33)	25 (19–30)	0.92
ALT (U/L)	32 (23–42)	34 (26–45)	35 (25–44)	0.29
NT-proBNP (pg/mL)	3,673 (1709–8,118)	2,217 (889–5,523)	1,694 (774–5,214)	<0.001
Therapy during hospitalization				
IV diuretic dose 24 h	250 (99–500)	165 (50–475)	125 (40–290)	<0.001
Nitrates	61 (24.5)	77 (30.9)	14 (15.7)	0.02
Inotropes	28 (11.2)	19 (7.6)	3 (3.4)	0.06
Therapy at discharge				
MRA	184 (73.9)	193 (77.5)	74 (83.1)	0.20
Furosemide	243 (97.6)	241 (96.8)	87 (97.8)	0.82
Furosemide dose (mg/die)	100 (50–175)	100 (50–125)	75 (25–125)	0.09

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT pro-BNP, N terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

[a]Congestion score calculated as the presence of two or more signs (peripheral oedema, pulmonary rales, and jugular vein distension).

Continuous variables shown as mean ± standard deviation, skewed variables as median (interquartile range), and dichotomous variables as count (%).

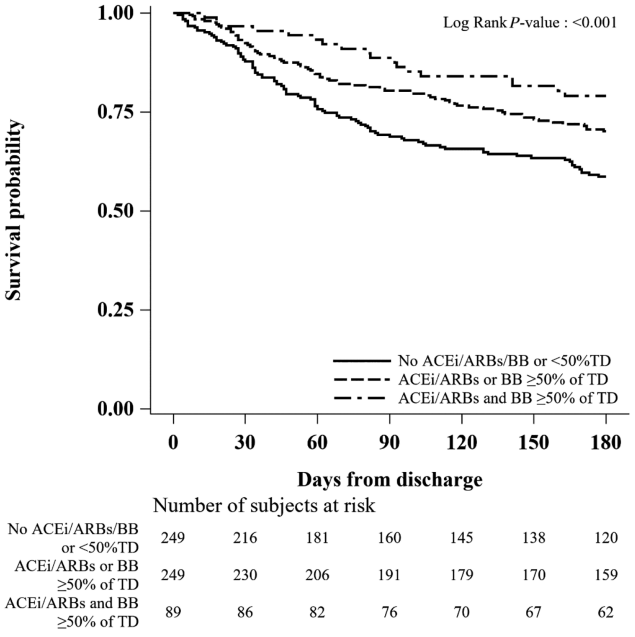
(log-rank P value 0.01). A trend towards a better prognosis was also observed in patients with stable therapy compared with those with decrease (log-rank P value 0.05). (*Table 4, Figure 3*).

At Cox regression analysis, treatment intensification was an independent predictor of improved outcomes compared with stable treatment (adjusted HR 0.49, 95% CI [0.29–0.83]; P = 0.01), whereas therapy decrease was not associated with worse prognosis after adjustment. Similar results were obtained regarding the individual analysis of ACEi/ARBs and BB, where the intensification of treatment resulted an independent predictor of better outcomes (*Table 5*).

Discussion

In this study, we sought to evaluate the prognostic impact of ACEi/ARBs and BB at discharge in a monocentric cohort of AHF patients with reduced left ventricular ejection fraction. We showed that treatment with ACEi/ARBs and/or BB ≥ 50% of TD was an independent predictor of better outcomes at 180 days compared with no or low-dose treatment, with an incremental benefit from single to dual drug optimal dose. In addition, we observed that treatment intensification from admission to discharge resulted in reduced rates of the composite primary endpoint at 180 days.

Figure 2 Kaplan–Meier plot for the combined endpoints of death or HF hospitalizations to Day 180, according to therapy at discharge (*N* = 587 with non-missing information). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptors blocker; BB, beta-blockers; TD, target dose.



The treatment of AHF remains a challenge for clinicians with high post-discharge event rates and no evidence of benefits coming from large clinical trials investigating novel drugs. The role of oral therapies as ACEi/ARBs and BB has been scarcely studied in this context, despite European guidelines strongly recommend to maintain these therapies during the hospitalization.[1] Data from the European registry show that despite an improvement of prescription rates from admission, only about 77% and 72% of inpatients are discharged on ACEi/ARBs or BB, respectively.[13] Our study is consistent with these data showing a prescription rate of about 76% for ACEi/ARBs and 85% for BB. However, only a small proportion (15.2%) of patients in this study reached the criteria of an optimal oral therapy and the 42% receive no or low-dose treatment confirming that there is still a large proportion of undertreated patients who may potentially benefit from therapy intensification.

The positive effect on prognosis of ACEi/ARBs and BB in the acute setting has been studied in registries, which showed that treatment with either ACEi/ARBs and BB or both is associated with a progressive better survival.[4,8] However, previous reports with few exceptions included mainly a qualitative assessment of therapy prescription and a quantitative evaluation of optimal therapy including drug dose was not tested. This is particularly important because data from the BIOSTAT registry showed that a dose $<$50% of TD has not been associated with outcomes improvement and conversely that the survival benefit of a dose $\geq$50% of TD is similar to the top dose regimen.[14] For this reason, compared with previous studies, we also considered the percentage of TD reached, according to the TD recommended in the European guidelines.[1] Our data support the hypothesis that an optimal treatment with ACEi/ARBs and BB at the time of discharge is safe and associated with markedly better outcomes during the vulnerable phase. To note, even suboptimal therapy with $\geq$50% of TD of ACEi/ARBs or BB was associated with an improvement of prognosis compared with no or low-dose therapy underscoring the importance to make any attempt to increase drug prescription and optimization in the acute setting. This was also confirmed by the fact that treatment intensification during the hospitalization resulted in better prognosis compared with stable therapy, whereas drug decrease showed only a trend towards worse outcomes, likely due to a major role of confounding factors related to disease severity and comorbidities. Patients who did not have therapy optimization likely suffered of a more advanced stage HF and/or had a higher burden of comorbidities, making difficult to introduce or uptitrate oral therapies, which may affect vital signs and renal function in the recovery phase after AHF. Notably, the crude rates of events doubled from patients who received ACEi/ARBs and BB at optimal dose to those without or with low therapy. This gap in outcomes probably cannot be solely explained by the effect of the disease modifying therapies, but also by an inherent increased patients' risk. To date, this is consistent with everyday clinical practice, and unfortunately, currently, there are no other therapeutic options for this subgroup, which is also frequently excluded by clinical trials and represents an urgent medical need in AHF.

Limitation

Our study has some limitations which deserve to be disclosed. First of all, this is a single-centre retrospective analysis based on a relatively small sample size, and thus, generalizability is limited. However, this study was performed in a tertiary and experienced centre for the treatment of AHF, and the monocentric design has the advantage to homogenize the criteria applied to therapy prescription. Being a retrospective analysis, some data could not be retrieved from records; in particular, details regarding the reason of non-prescription were not uniformly collected and were not included in the present analysis. Another limit is that only ACEi/ARBs and BB were considered despite most of the patients have also an indication for a mineralocorticoid receptor antagonist (MRA). However, including MRA to the current analysis would have further stratified our

Table 3 Patients characteristics according to changes in therapy from admission to discharge ($N = 578$ with non-missing information)

	Decreased $N = 258$	Stable $N = 194$	Increased $N = 126$	P
General characteristics				
Age (years)	70.9 ± 11.7	66.8 ± 10.7	66.3 ± 11.0	<0.001
Sex, male	202 (78.3)	178 (91.8)	114 (90.5)	<0.001
BMI (kg/m^2)	24.6 ± 4.3	26.0 ± 4.7	26.1 ± 5.5	0.01
NYHA Class III/IV	78 (30.2)	35 (18.0)	27 (21.4)	0.01
Congestion score ≥2[a]	42 (16.3)	16 (8.2)	16 (12.7)	0.04
SBP (mmHg)	109.4 ± 15.9	112.4 ± 17.1	111.6 ± 17.2	0.14
HR (bpm)	69.9 ± 10.9	67.5 ± 9.8	68.6 ± 10.9	0.06
LVEF (%)	25.9 ± 6.9	25.7 ± 6.9	25.7 ± 7.5	0.97
ICD	102 (39.5)	78 (40.2)	41 (32.5)	0.33
CRT	76 (29.5)	40 (20.6)	31 (24.6)	0.10
HF aetiology				
Idiopathic dilated cardiomyopathy (%)	106 (41.1)	80 (41.2)	57 (45.2)	0.26
Ischaemic cardiomyopathy (%)	147 (57.0)	109 (56.2)	62 (49.2)	
Hypertensive cardiomyopathy (%)	5 (1.9)	5 (2.6)	7 (5.6)	
Medical history				
Previous HF	190 (73.6)	157 (80.9)	95 (75.4)	0.19
Diabetes mellitus	74 (28.7)	65 (33.5)	49 (38.9)	0.13
Arterial hypertension	119 (46.1)	116 (59.8)	74 (58.7)	0.01
Atrial fibrillation	105 (40.7)	74 (38.1)	53 (42.1)	0.76
COPD	63 (24.4)	30 (15.5)	28 (22.2)	0.06
CKD	131 (50.8)	64 (33.0)	49 (38.9)	0.001
Laboratory				
Hb (g/dL)	12.5 ± 1.8	12.8 ± 1.8	12.9 ± 1.9	0.02
Serum creatinine (mg/dL)	1.5 (1.2–2.1)	1.3 (1.0–1.8)	1.4 (1.0–1.8)	0.001
eGFR (mL/min/1.73 m^2)	44.0 (31.4–59.7)	54.0 (39.5–75.0)	53.3 (40.8–76.2)	<0.001
Sodium (mEq/L)	139.1 ± 4.3	139.5 ± 4.2	138.7 ± 3.4	0.26
Bilirubin (mg/dL)	0.77 (0.57–1.10)	0.80 (0.57–1.04)	0.80 (0.54–1.03)	0.87
AST (U/L)	24 (18–35)	23 (18–32)	26 (19–36)	0.44
ALT (U/L)	32 (23–43)	32 (25–41)	40 (28–58)	0.01
NT-proBNP (pg/mL)	3,304 (1,599–7,138)	1905 (799–5,578)	2,254 (1,089–5,058)	0.004
Therapy during hospitalization				
IV diuretic dose 24 h	250 (100–500)	125 (40–450)	163 (50–350)	<0.001
Nitrates	63 (24.4)	48 (24.7)	36 (28.6)	0.66
Inotropes	30 (11.6)	11 (5.7)	9 (7.1)	0.07
Therapy at discharge				
MRA	193 (74.8)	154 (79.4)	98 (77.8)	0.51
Furosemide	252 (97.7)	191 (98.5)	119 (94.4)	0.09
Furosemide dose (mg/die)	100 (50–175)	75 (50–125)	75 (50–125)	0.09

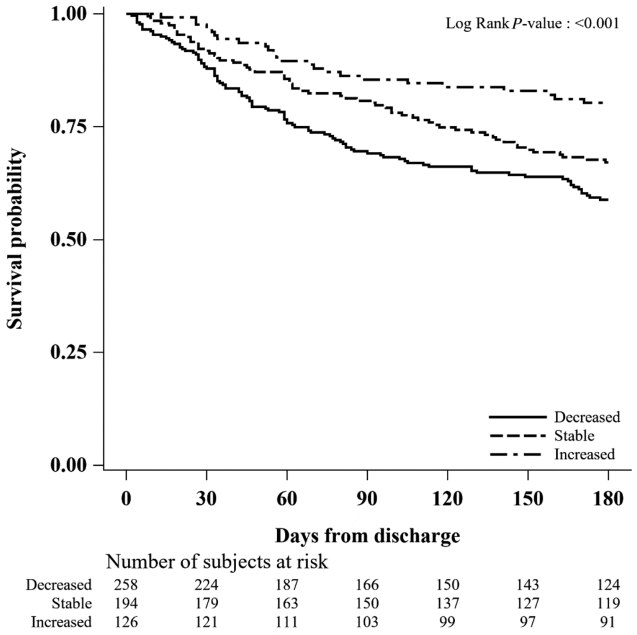
ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HF, heart failure; HR, heart rate; ICD, implantable cardioverter-defibrillator; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT pro-BNP, N terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.
[a]Congestion score calculated as the presence of two or more signs (peripheral oedema, pulmonary rales, and jugular vein distension).
Continuous variables shown as mean ± standard deviation, skewed variables as median (interquartile range), dichotomous variables as count (%).

Table 4 Events to Day 180 after discharge, overall ($N = 623$) and by strata of therapy at discharge ($N = 587$ with non-missing information) and of therapy changes from admission to discharge ($N = 578$ with non-missing information)

		Therapy at discharge			Therapy changes from admission to discharge		
	Overall $N = 623$	No ACEi/ARBs/BB or <50%TD $N = 249$	ACEi/ARBs or BB ≥ 50% of TD $N = 249$	ACEi/ARBs and BB ≥ 50% of TD $N = 89$	Decreased $N = 258$	Stable $N = 194$	Increased $N = 126$
Death or HF hospitalization, *N* (%)	193 (31.0)	97 (39.0)	72 (28.9)	18 (20.2)	100 (38.8)	62 (32.0)	24 (19.0)
Death, *N* (%)	59 (9.5)	34 (13.7)	16 (6.4)	6 (6.7)	34 (13.2)	17 (8.8)	5 (4.0)
HF hospitalization, *N* (%)	170 (27.3)	82 (32.9)	67 (26.9)	16 (18.0)	85 (32.9)	57 (29.4)	22 (17.5)

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BB, beta blocker; HF, heart failure; TD, target dose.
Data shown as count (%).

Figure 3 Kaplan–Meier plot for the combined endpoints of death or heart failure hospitalizations to Day 180, according the variation of therapy from admission to discharge (N = 578 with non-missing information).



sample, and recent data from the GREAT registry showed that MRA is not associated with a clear benefit in early post-hospitalization period.[4] The use of other HF medications as ivabradine was not included in the analysis due to the paucity of patients who received it, as well as sacubitril–valsartan because no patient included in this analysis was on treatment.

Inherent limitations related to analysis of treatment prescription are the possible changes in therapy that occurred from discharge to the end of follow-up. Patients may undergo major changes in treatment after discharge, and lack of data on post-discharge changes is a major limitation of our study. However, we believe that this impact would be limited considering the short follow-up period and evidences showing that after an hospitalization for AHF, most patients do not change significantly the treatment.[20]

Finally, subgroups analysis was not performed due to the small sample size, which would not allow to have sufficient groups for making meaningful comparison. In particular, no gender-related analysis was carried out although we observed a larger proportion of females in the no/low prescription group, and as demonstrated by recent data from the BIOSTAT registry, the effective dose in this sub-population could be lower.[21]

Conclusion

In patients with reduced LVEF discharged for AHF, the adherence to ACEi/ARBs and BB prescription at discharge is still suboptimal especially in older subjects with a more advanced stage of HF and comorbidities. Patients treated at discharge with at least 50% of TD of ACEi/ARB and/or BB showed an independent lower risk of all-cause death and HF rehospitalization in the post-discharge vulnerable phase. Finally, the intensification of treatment with ACEi/ARBs and BBs throughout the hospitalization resulted in better outcomes.

Table 5 Cox regression analysis for the combined endpoints of death or HF hospitalization to Day 180

	Level	Unadjusted HR (95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*
Therapy at discharge					
Therapy group ref: no ACEi/ARBs/BB or <50%TD	ACEi/ARBs or BB ≥ 50% of TD	0.66 (0.48–0.89)	0.01	0.69 (0.49–0.98)	0.04
	ACEi/ARBs and BB ≥ 50% of TD	0.43 (0.26–0.70)	<0.001	0.54 (0.30–0.96)	0.03
ACEi/ARBs ref: no ACEi/ARBs	<50% TD	1.37 (1.00–1.88)	0.05	0.83 (0.54–1.26)	0.37
	≥50% TD	0.56 (0.35–0.90)	0.02	0.59 (0.38–0.91)	0.02
BB ref: no BB	<50% TD	0.82 (0.56–1.22)	0.33	0.91 (0.57–1.45)	0.69
	≥50% TD	0.63 (0.41–0.98)	0.04	0.79 (0.47–1.31)	0.35
Therapy changes from admission to discharge					
Therapy change ref: Stable	Decreased	1.37 (1.00–1.88)	0.05	1.21 (0.84–1.73)	0.31
	Increased	0.56 (0.35–0.90)	0.02	0.49 (0.29–0.83)	0.01
ACEi/ARBs ref: Stable % TD	Decreased	1.24 (0.90–1.70)	0.19	0.98 (0.68–1.42)	0.91
	Increased	0.59 (0.40–0.88)	0.01	0.56 (0.36–0.88)	0.01
BB ref: stable % TD	Decreased	0.93 (0.64–1.35)	0.71	0.95 (0.62–1.46)	0.82
	Increased	0.56 (0.40–0.78)	<0.001	0.60 (0.41–0.87)	0.01

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, beta blocker; CI, confidence interval; HR, hazard ratio; TD, target dose.
[a]Adjusted for age, sex, chronic obstructive pulmonary disease, ischaemic cardiomyopathy, body mass index, systolic blood pressure, haemoglobin, and estimated glomerular filtration rate.

Conflict of interest

V. C. received consulting honoraria from CVie Therapeutics Limited, Servier, and Windtree Therapeutics. M. M. reports personal consulting honoraria from Bayer, Novartis, Fresenius, Servier, and Windtree Therapeutics for participation to advisory board meetings and executive committees of clinical trials. All the other authors have nothing to disclose.

Supporting information

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

Table S1. Oral therapy at admission and at discharge (N = 623)

Figure S1. Box plot of ACEi/ARBs (panel A) and of BB (panel B) percentage of the target dose taken at admission, on the left, and at discharge, on the right (N = 623)

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