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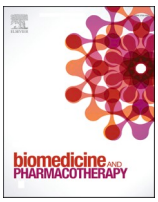

Already low drug dose antagonism of the renin-angiotensin aldosterone system decreases 1-year mortality and rehospitalization in old heart failure patients

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ABSTRACT

Aims: Hospitalization for heart failure treatment (HHF) is an incisive event in the course of HF. Today, the large majority of HHF patients is ≥ 65 years and discharge HF drugs are most often not applied at dose levels acknowledged to provide prognostic benefit. This study therefore aims to investigate the treatment effect size of discharge HF drugs in old HHF patients.
Methods: Drugs are analyzed according to pharmacological class. Individual discharge HF drug dose is reported as percentage of guidelines-recommended target dose. Primary endpoint was 1-year all-cause mortality (ACM) after discharge; the secondary endpoint combined 1-year ACM and first cardiovascular hospitalization within 1 year after discharge. Comparison between 65–80 years and > 80 years old study participants tested the relative treatment effect size as a function of respective age group.
Results: The 875 consecutive HHF patients had a median age of 82 years [76–87 years]; 48.6 % were females. Betablocker and diuretic treatment did not change the incidence of endpoints. Inhibition of the renin-angiotensin system (RASi), when compared to no treatment, decreased the incidence of endpoints both at the 1–25 % and the > 25 % target dose level. Antagonists of the mineralocorticoid receptor (MRA), when compared to no treatment, decreased the secondary endpoint at the 1–25 % target dose level but not at the > 25 % target dose level. The relative treatment effect size of RASi or MRA corresponded between the age strata for both endpoints.
Conclusion: Low-dose RASi and MRA had beneficial effects in these old HHF patients.

1. Introduction

Acute heart failure precipitates millions of hospital admissions per year [1]. Today, the large majority of patients hospitalized for HHF are old with a mean age of 81–83 years in contemporary cohorts [2–4] while patients in former study populations were younger (69–74 years) [1].

In stable chronic HFrEF, randomized controlled trials established betablockade, ACEi or ARB (RASi), MRA and recently SGLT2 inhibition for reduction of cardiovascular mortality and morbidity [5]. These drugs are also effective in chronic HFmrEF [5,6] while in stable chronic HFpEF with an LVEF < 60 % only the SGLT2 inhibitor empagliflozin is shown to provide an immediate prognostic benefit [6]. Betablockers, RASi, and MRAs are nonetheless applied in HFpEF patients mostly for cardiovascular indication such as arterial hypertension or renal preservation [5].

Abbreviations: ACEi, angiotensin converting enzyme inhibition; ACM, all-cause mortality; ARB, angiotensin II receptor blocker; AHF, acute heart failure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HHF, hospitalization for treatment of AHF; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly-reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineral-corticoid receptor antagonist; old, 65–80 years; RASi, renin-angiotensin system inhibition; very old, > 80 years.

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This explains why contemporary HHF registries demonstrate almost equal administration of all these drugs in acute HF patients with reduced, mildly-reduced, or preserved LVEF [1–4,7].

In HFrEF patients, actual guidelines recommend uptitration of HF drugs to target dose in order to achieve significant reduction of mortality and morbidity [5,8]. In analogy, the dose of HF drugs is often progressively increased in patients with chronic HFmrEF or HFpEF. However, substantial non-prescription as well as underdosing of HF drugs are reported from contemporary registries following old (65–80 years) and very old HF patients (> 80 years) [9,10].

The prognostic benefit of underdosed treatment is questionable [5,8]. Therefore, this observational study investigated the treatment effect size of discharge HF drug treatment in consecutive HHF patients of ≥ 65 years. HF drug treatment was analyzed as a function of the pharmacological class and the percentage of guidelines-recommended target dose. Applied outcome measures were the primary endpoint 1-year ACM after discharge and the secondary endpoint composed of 1-year ACM or first cardiovascular rehospitalization after discharge.

2. Methods

2.1. Study aims

This study investigated in consecutive HHF patients the individual treatment effect size as a function of the percentage of guidelines-recommended target HF drug dose at the day of discharge [5]. Because of the distribution of the percentage of guidelines-recommended target dose, study participants were grouped into patients i) without any (0 %), ii) 1–25 %, and iii) > 25 % of guidelines-recommended target dose for betablockers, RASi, MRA, or loop diuretics.

1. The ***first aim*** compared demographic, clinical, echocardiographic, biological parameters, cardiovascular risk factors, number of prescriptions and dosing of HF drugs in patients with or without 1-year ACM.
2. The ***second aim*** investigated the treatment effect size of betablockers, RASi, MRA or loop diuretics on the primary endpoint 1-year all-cause mortality (ACM), and on the secondary endpoint composed of 1-year ACM or first cardiovascular hospitalization during the first year after the index visit. For the secondary endpoint, study participants were censored after first occurrence of either component.
3. The ***third aim*** studied the treatment effect size of betablockers, RASi, MRA, or loop diuretics on both endpoints in study patients aged 65–80 or > 80 years.

2.2. Study population

This mono-center prospective observational study included 875 consecutive HHF patients. Recruited study participants were [1] ≥ 65 years old, had [2] HHF treatment at the Lausanne University Hospital with [3] transthoracic echocardiography during index hospitalization, and had provided [4] written consent. Excluded were patients with HF due to acute ST-elevation myocardial infarction, acute non-ST-elevation myocardial infarction, complex congenital heart disease, acute pulmonary embolism, or when concomitant comorbidity was considered to reduce survival time to less than 1 year. Furthermore, HF patients were excluded when HF was primarily related to exacerbation of COPD, metabolic, toxic or infectious disorder.

The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee (CER Vaud 1158/19).

2.3. Acquisition of anthropometric, biological, and clinical data

Data were collected from the individual patient's electronic health report at the Lausanne University Hospital (NS,TA). Accuracy was confirmed by revisiting all patients' data revealing 99.7 % correctness (NS). Comprehensive transthoracic echocardiography was always acquired on GE Healthcare machines by board-certified cardiologists. LVEF was quantitatively assessed using the biplane Simpson method; the severity of valvular regurgitation was graded using multiparametric assessment [11]. One-year ACM was collected via extraction of the Swiss registry of deaths and calculated as of the day of hospital discharge; cardiovascular rehospitalization was documented by patient's electronic health report.

2.4. Statistical analysis

Demographic, clinical, biological, echocardiographic, cardiovascular risk factor parameters and drug intake as well as the MAGGIC risk score [12] were described with the absolute number accompanied by the relative number in case of categorical variables, or the median accompanied by the 25th–75th percentile (interquartile range, IQR) in case of continuous variables.

We compared continuous variables between survivors and non-survivors (as well as between the two age strata 65–80 years vs. > 80 years) with the Wilcoxon rank sum test. Continuous variables of the 3 target dose groups (0 % vs. 1–25 % vs. > 25 %) were compared for each pharmacological class of HF drugs using the Kruskal-Wallis test.

Categorical variables between studied groups (survivors and non-survivors, age-groups as well as the three percentage groups of target dose groups) were compared with the Chi-squared test.

Univariable Cox regression established the relation of all parameters with the primary endpoint. Multivariable Cox regression analysis evaluated the impact of the 3 %target dose strata of the four studied HF drug classes (betablockers, RASi, loop diuretic, and MRA) on the primary or secondary endpoint. The strength of association was quantified with the hazard ratio (HR) and the 95 % confidence interval (CI).

The relationship between the percentage of maximal target dose and the primary or the secondary endpoint was established in multivariable model 1 which was adjusted using the MAGGIC risk score (model 1). This adjustment was chosen because this well-acknowledged score calculates the risk of case fatality in individual HF patients on the basis of 13 parameters and granular weighting of LVEF [12]. For sensitivity analysis, multivariable model 2 investigated the same relationship but adjusted on all study parameters associated with 1 year-ACM ($p < 0.05$) in univariable analysis on the condition that variables were without collinearity with other variables (i.e. RDW with the collinearity with hemoglobin) (model 2). Results of these analyses were considered robust when corresponding in both models.

Last, the interaction effect of different target dose groups was evaluated in all patients and in the age groups (65–80 vs. > 80 years) presenting the hazard ratios (HR). No adjustment of multiple testing was performed.

The statistical analyses were performed using STATA®16.1 (Stata Corp, the College Station, Texas, USA).

3. Results

3.1. Comparison of study patients with or without 1-year ACM

Table 1 shows that patients with 1-year ACM (n = 275; 31.7 %) were older (median 85 vs. 81 years; $p < 0.001$) and by trend more often males. Furthermore, median BMI, systolic and diastolic blood pressure were lower while the MAGGIC score was higher in patients with case-fatality. The prevalence of COPD, cardiovascular disease, and atrial fibrillation was not significantly different between the groups; arterial hypertension, dyslipidemia, and by trend diabetes were less prevalent in patients with case-fatality.

In patients with 1-year ACM, the indexed diameter of the left ventricle at end-diastole or the left atrium was higher and mild to

Table 1
Comparison of demographic and clinical parameters of study patients with or without 1-year ACM after discharge from heart failure hospitalization.

	No.	All		1-year ACM				
				Yes	($n = 275$)	No	($n = 600$)	*P*-value
DEMOGRAPHICS								
Age [y]	875	82	[76–87]	85	[79–89]	81	[75–86]	< 0.001
Age group	875	82	[76–87]	85	[79–89]	81	[75–86]	< 0.001
65–80 y		352	[40.2]	75	[27.3]	277	[46.2]	
> 80 y		523	[59.8]	200	[72.7]	323	[53.8]	< 0.001
Female gender	875	425	[48.6]	122	[44.4]	303	[50.5]	0.092
CLINICAL PARAMETERS								
BMI [kg/m^2]	867	26.0	[22.8–30.0]	24.5	[22.0–27.3]	26.7	[23.4–31.3]	< 0.001
SBP [mmHg] discharge	863	125	[111–140]	120	[107–137]	128	[114–140]	< 0.001
DBP [mmHg] discharge	863	67	[59–75]	65	[56–75]	68	[60–76]	0.004
HR [bpm] discharge	862	78	[69–88]	76	[68–86]	79	[70–88]	0.057
MAGGIC score	875	24	[21–27]	26	[23–29]	23	[20–26]	< 0.001
CARDIOVASCULAR RISK FACTORS								
COPD	875	173	[19.8]	56	[20.4]	117	[19.5]	0.766
Smoking status	875	411	[47.0]	126	[45.8]	285	[47.5]	0.644
CVD	875	419	[47.9]	138	[50.2]	281	[46.8]	0.357
Hx of AFib	875	526	[60.1]	176	[64.0]	350	[58.3]	0.112
Dyslipidemia	875	460	[52.6]	126	[45.8]	334	[55.7]	0.007
Hypertension	875	743	[84.9]	219	[79.6]	524	[87.3]	0.003
Diabetes mellitus	875	288	[32.9]	78	[28.4]	210	[35.0]	0.052
QRS duration [ms]	869	90	[80–120]	90	[80–120]	90	[80–120]	0.716
ECHOCARDIOGRAPHY MEASURES								
LVEDDi [mm/m^2]	666	29	[25–32]	30	[26–33]	28	[25–32]	0.048
LVMi [g/m^2]	634	112	[87–136]	118	[91–138]	110	[86–133]	0.122
LADi [mm/m^2]	616	25	[23–28]	26	[24–29]	25	[22–28]	0.031
LVEF [%]	875	45	[35–60]	45	[30–60]	47	[35–60]	0.112
Mitral regurgitation	875	680	[77.7]	220	[80.0]	460	[76.7]	0.271
Mitral stenosis	875	19	[2.2]	6	[2.2]	13	[2.2]	0.989
Aortic regurgitation	875	342	[39.1]	112	[40.7]	230	[38.3]	0.500
Aortic stenosis	875	148	[16.9]	64	[23.3]	84	[14.0]	0.001
Tricuspid regurgitation	875	436	[49.8]	145	[52.7]	291	[48.5]	0.246
BIOLOGICAL PARAMETERS								
Hemoglobin [g/l]	875	121	[107–136]	120	[105–134]	122	[108–137]	0.036
Hematocrit [%]	873	37	[33–41]	37	[33–41]	37	[33–41]	0.152
RDW [%]	875	15	[14–16]	16	[15–17]	15	[14–16]	< 0.001
Leucocytes [G/l]	875	8	[7–11]	9	[7–12]	8	[7–11]	0.182
Glucose [mmol/l]	859	7.1	[6.1–9.0]	6.9	[5.9–8.5]	7.2	[6.2–9.2]	0.024
Creatinine [μmol/l]	875	112	[85–152]	124	[92–174]	107	[82–143]	< 0.001
Sodium [mmol/l]	875	140	[137–142]	140	[136–142]	140	[137–142]	0.155
Potassium [mmol/l]	875	4.3	[4.0–4.7]	4.3	[4.0–4.7]	4.3	[3.9–4.7]	0.310
Cholesterol [mmol/l]	701	4.0	[3.3–4.7]	3.9	[3.1–4.7]	4.0	[3.3–4.7]	0.461

[interval] = IQR or [number] = %; ACM = all-cause mortality; AFib/Flutter = atrial fibrillation/flutter; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; HR = heart rate; Hx = history; ICD = internal cardioverter defibrillator; LADi = left atrial diameter index; LVEDD = left ventricular enddiastolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; MAGGIC = Meta Analysis Global Group in Chronic Heart Failure; RDW = red cell distribution width; SBP = systolic blood pressure.

Table 2
Discharge drug treatment of study patients with or without 1-year ACM.

	Total			1-year ACM				
				Yes	($n = 275$)	No	($n = 600$)	*p*-value
MEDICAL HF TREATMENT								
Betablocker (number, %)	875	414	[47.3]	122	[44.4]	292	[48.7]	0.237
ACE-I (number, %)	875	294	[33.6]	94	[34.2]	200	[33.3]	0.805
ARB (number, %)	875	238	[27.2]	60	[21.8]	178	[29.7]	0.015
ARNI (number, %)	875	1	[0.1]	0	[0.0]	1	[0.2]	0.498
MRA (number, %)	875	101	[11.5]	40	[14.5]	61	[10.2]	0.060
Loop diuretics (number,%)	875	510	[58.3]	192	[69.8]	318	[53.0]	< 0.001
ICD	875	96	[11.0]	30	[10.9]	66	[11.0]	0.968
% MAXIMAL DOSE HF TREATMENT								
Beta-blocker		12.5	[0.0–25.0]	6.2	[0.0–25.0]	12.5	[0.0–25.0]	< 0.001
MRA	869	0.0	[0.0–0.0]	0.0	[0.0–0.0]	0.0	[0.0–0.0]	0.047
ACE-I/ARB	875	14.3	[0.0–31.2]	0.0	[0.0–21.4]	14.3	[0.0–50.0]	< 0.001
Loop diuretics	834	50.0	[25.0–100.0]	50.0	[25.0–100.0]	50.0	[25.0–83.3]	0.229
OTHER DRUG TREATMENT								
Oral antidiabetic drugs	875	132	[15.1]	29	[10.5]	103	[17.2]	0.011
Insulin	875	129	[14.7]	36	[13.1]	93	[15.5]	0.351
Statin (number, %)	875	348	[39.8]	96	[34.9]	252	[42.0]	0.047

ACE-I = angiotensin converting enzyme inhibition; ACM = all-cause mortality; ARB = angiotensin II receptor blocker; ARNI = angiotensin II receptor and neprilysin inhibition; HF = heart failure; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist.

moderate aortic stenosis was more prevalent; other echocardiographic parameters were not significantly different. Hemoglobin and glucose levels were lower while RDW was higher in cases with fatality.

The univariable Cox regression analysis for all variables with 1-year ACM is shown in Supplementary Table 5.

3.2. Discharge drug treatment in study participants with or without 1-year ACM

Table 2 shows that administration of betablockers, RASi, MRA or internal cardiac defibrillator therapy did not differ significantly between study participants with or without 1-year ACM. However, when the percentage of guidelines-recommended target dose was investigated, study patients with 1-year ACM were significantly more often treated with loop diuretics while discharge drug dose was lower for beta-blockers, RASi, and MRA. Furthermore, patients with 1-year ACM were at discharge less often on oral antidiabetic or statin treatment.

3.3. Characteristics and incidence of endpoints in percentage of target dose groups

Supplementary Tables 1–4 present for each pharmacological class the comparison of the characteristics between patients with no treatment, or treatment with 1–25 % or > 25 % of target dose. Median age and the MAGGIC score were highest in study participants without RASi, betablocker or MRA treatment; for loop diuretic treatment age was highest in the 1–25 % stratum.

Overall, when compared to admission, more study participants were at discharge on loop diuretic treatment (+ 24.5 %) while the increase was less important for betablockers (+ 14.1 %), RASi (+ 7 %), and MRA (+ 6.2 %). The incidence of 1-year ACM and 1-year CV hospitalization was always higher in the > 80 years group (Supplementary Table 6).

3.4. Impact of the discharge drug dose on the primary or secondary endpoints

Tables 3, 4 and Supplementary Table 7 present univariable Cox regression analysis and multivariable models of the primary and the secondary endpoint analyzed as a function of the percentage strata of HF-drug target dose. In addition, percentage target dose strata were analyzed for all study participants, as well as for age strata 65–80 years and > 80 years. The graphical abstract shows the respective associations as a Forest plot.

3.4.1. Treatment size effect of percentage target drug dose in the total study population

Supplementary Table 7 and the graphical show that RASi reduces the HR of the primary and secondary endpoints in the strata 1–25 % or > 25 % of target dose when compared to no RASi. Of note, the HR is descriptively smaller for the > 25% stratum when compared with the 1–25 % stratum. In addition, there is a beneficial effect for the secondary endpoint when patients receive MRA treatment at 1–25 % of target dose while this effect failed to reach significance when the percentage of target MRA dose was > 25 % (Table 4).

3.4.2. Treatment size effect of percentage target drug dose in age groups 65–80 and > 80 years

Betablocker treatment was not associated with a change of the

Table 3
Treatment effect size of discharge target doses (TD) on A.) primary and B) secondary endpoint in study participants of 65–80 years age (n = 352) using Cox Regression.

		Univariable			Multivariable Model 1*			Multivariable Model 2#		
		HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value
A.										
	Betablocker									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	0,78	[0.47–1.29]	0,335	1,03	[0.62–1.72]	0,909	0,64	[0.37–1.11]	0,11
	TD > 25 %	0,52	[0.27–1.02]	0,057	0,82	[0.41–1.64]	0,582	0,71	[0.35–1.47]	0,363
	ACE-I/ARB									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1– 25 %	0,61	[0.36–1.03]	0,064	0,67	[0.39–1.13]	0,132	0,44	[0.24–0.82]	0,01
	TD > 25 %	0,27	[0.15–0.47]	< 0.001	0,35	[0.2–0.63]	< 0.001	0,29	[0.16–0.53]	< 0.001
	Loop diuretic									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	0,49	[0.22–1.06]	0,068	0,47	[0.21–1.01]	0,053	0,45	[0.2–0.99]	0,046
	TD > 25 %	0,67	[0.38–1.17]	0,156	0,53	[0.3–0.92]	0,025	0,43	[0.23–0.82]	0,01
	MRA									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	1,04	[0.47–2.28]	0,921	0,99	[0.45–2.17]	0,977	0,41	[0.17–0.99]	0,048
	TD > 25 %	0,71	[0.36–1.39]	0,313	0,81	[0.41–1.6]	0,55	0,66	[0.32–1.34]	0,249
B.										
	Betablocker									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	1,04	[0.71–1.51]	0,843	1,24	[0.85–1.81]	0,266	1,01	[0.68–1.51]	0,942
	TD > 25 %	0,79	[0.5–1.25]	0,32	1,05	[0.65–1.68]	0,847	0,94	[0.58–1.53]	0,798
	ACE-I/ARB									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	0,53	[0.35–0.8]	0,003	0,55	[0.36–0.83]	0,004	0,43	[0.27–0.69]	< 0.001
	TD > 25 %	0,43	[0.29–0.63]	< 0.001	0,48	[0.33–0.71]	< 0.001	0,39	[0.25–0.59]	< 0.001
	Loop diuretic									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	0,9	[0.51–1.58]	0,713	0,85	[0.49–1.5]	0,584	0,78	[0.44–1.39]	0,4
	TD > 25 %	1,12	[0.72–1.74]	0,624	0,99	[0.63–1.55]	0,974	0,69	[0.42–1.13]	0,142
	MRA									
	TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
	TD = 1–25 %	0,66	[0.35–1.27]	0,216	0,61	[0.32–1.17]	0,139	0,44	[0.22–0.89]	0,023
	TD = 1–25 %	0,71	[0.44–1.13]	0,148	0,75	[0.47–1.2]	0,228	0,67	[0.41–1.09]	0,107

Adjusted on the *MAGGIC score, #age, sex, hypertension, dyslipidemia, Hx of AFib/AFlutter, LVEF, aortic stenosis, statin, ARNI, loop diuretics on arrival, oral antidiabetics, SBP and DBP on arrival, RDW, creatinine, hemoglobin.

Table 4
Treatment effect size of discharge target doses (TD) on A) primary and B) secondary endpoint in study participants > 80 years (= 523) using Cox-Regression.

	Univariable			Multivariable Model 1*			Multivariable Model 2#		
	HR	95 % CI	p-value	HR	95 % CI	p-value	HR	95 % CI	p-value
A.									
Betablocker									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	0,72	[0.53–0.99]	0,041	0,83	[0.61–1.14]	0,249	0,76	[0.54–1.06]	0,102
TD > 25 %	0,47	[0.29–0.76]	0,002	0,64	[0.39–1.05]	0,079	0,56	[0.34–0.93]	0,025
ACE-I/ARB									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	0,5	[0.36–0.7]	< 0.001	0,49	[0.35–0.68]	< 0.001	0,48	[0.34–0.68]	< 0.001
TD > 25 %	0,43	[0.3–0.62]	< 0.001	0,45	[0.31–0.65]	< 0.001	0,49	[0.33–0.71]	< 0.001
Loop diuretic									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	1,05	[0.64–1.73]	0,837	0,98	[0.6–1.62]	0,951	0,81	[0.48–1.36]	0,416
TD > 25 %	1,11	[0.72–1.71]	0,632	0,98	[0.63–1.51]	0,913	0,74	[0.46–1.19]	0,211
MRA									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	0,42	[0.13–1.32]	0,137	0,35	[0.11–1.09]	0,069	0,33	[0.1–1.06]	0,062
TD > 25 %	0,91	[0.53–1.53]	0,713	0,93	[0.55–1.57]	0,786	0,83	[0.48–1.44]	0,518
B.									
Betablocker									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	0,97	[0.75–1.24]	0,786	1,1	[0.85–1.42]	0,488	0,97	[0.74–1.27]	0,831
TD > 25 %	0,84	[0.6–1.19]	0,328	1,07	[0.75–1.54]	0,7	0,89	[0.62–1.28]	0,528
ACE-I/ARB									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	0,67	[0.51–0.87]	0,002	0,65	[0.5–0.85]	0,001	0,61	[0.46–0.8]	< 0.001
TD > 25 %	0,52	[0.39–0.7]	< 0.001	0,53	[0.4–0.72]	< 0.001	0,54	[0.4–0.74]	< 0.001
Loop diuretic									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	1,31	[0.87–1.96]	0,197	1,26	[0.84–1.89]	0,263	1,09	[0.71–1.66]	0,705
TD > 25 %	1,31	[0.92–1.87]	0,138	1,2	[0.84–1.72]	0,316	0,96	[0.66–1.42]	0,853
MRA									
TD = 0 %	1	[baseline]		1	[baseline]		1	[baseline]	
TD = 1–25 %	0,44	[0.18–1.08]	0,073	0,39	[0.16–0.95]	0,039	0,35	[0.14–0.86]	0,022
TD > 25 %	1,04	[0.69–1.57]	0,851	1,03	[0.69–1.56]	0,879	0,94	[0.61–1.44]	0,776

Adjusted on the *MAGGIC score, #age, sex, hypertension, dyslipidemia, Hx of AFib/AFlutter, LVEF, aortic stenosis, statin, ARNI, loop diuretics on arrival, oral antidiabetics, SBP and DBP on arrival, RDW, creatinine, hemoglobin.

hazard for both endpoints in both age strata.

RASi was associated with significant decrease of the risk for the primary endpoint in patients at > 25 % percentage of target drug dose in the 65–80 years group but not at the 1–25 % target dose level while both percentage target dose strata decreased the hazard for the secondary endpoint in this age group (Table 3). RASi was associated with a decrease of the hazard for both endpoints in study participants > 80 years old (Table 4).

Loop diuretic treatment was associated with a decrease of the risk for the primary but not the secondary endpoint in study participants 65–80 years of age (Table 3). In study participants with > 80 years of age, loop diuretic treatment was not associated with a change of the risk of either endpoint (Table 4).

MRA treatment was associated with a reduced hazard for the secondary endpoint in study participants > 80 years old when at the 1–25 % target dose level (Table 4). Otherwise, it was not related with the hazard for either endpoint in the younger age stratum or the primary endpoint in the very old stratum (Tables 3, 4).

4. Discussion

This study investigated in a study population of consecutive HHF patients with a mean age of 82 years the treatment effect size of HF-drug dose at discharge as a function of the primary endpoint 1-year ACM and the composite secondary endpoint 1-year ACM or cardiovascular rehospitalization. The most important result of this study is that in all study participants already small dose RASi is related with a decrease of the incidence of the primary and secondary endpoint when compared to no treatment. Likewise, MRA treatment is related with a decrease of the secondary endpoint when applied at the 1–25 % level of the guidelines-recommended target dose but not at higher percentage level. Betablocker treatment is not associated with a change of the incidence of both endpoints while loop diuretics are associated with a reduced risk for the primary endpoint in HHF patients 65–80 years of age. Overall, the impact of the four investigated 4 pharmacological classes on the primary and secondary outcomes showed corresponding treatment size efficacy in both the age strata.

The present cohort had excluded HF patients < 65 years of age in order to focus on the treatment effect size of HF drugs in old HHF patients. The mean age of the present study population cohort was nonetheless 82 years and therefore compares to the mean age (80–83 years) reported from other contemporary HHF cohorts [2–4,7]. This very old age suggests that the number of younger HHF patients has substantially decreased when compared with former cohorts [1] and this development underlines the need for studies in this age group.

Reasons for this increase of the portion of old patients are multifold but aging of the general population is foremost. Aging is associated with a disproportional increase of incident HF in the general population with a twofold increment in men and threefold increment in females for each decade of lifetime after the age of 65 years [13]. Moreover, treatment improvement has increased 5-years survival with HF from 29.1 % in the years 1970–1979 to 59.7 % in 2000–2009 [14] resulting in longer living with HF. Basis for this improved survival with HF, and particular with HFrEF, is the rigorous testing of candidate molecules in randomized controlled multicenter studies and the broad application of the combination of these molecules [5].

However, less than one third of study participants were above 75 years in landmark HFrEF trials [5,15,16] and very few studies had

focused on old patients [17–19]. This limitation also applies for HFpEF where the mean age in randomized controlled trials of HFpEF ranges between 67 and 75 years [20] while the mean age is 79–82 years in cohorts following chronic stable HFpEF patients or HFpEF patients after HHF [2–4,7,21,22]. In fact, drug treatment in the old patient faces important limitations due to altered pharmacokinetics from reduced hepatic first-pass effect, decreased clearance, and smaller total body water content [23]. Furthermore, the load of cardiovascular and non-cardiovascular comorbidity increases progressively with age [10, 24,25] and the resulting polypharmacy is associated with a high risk of adverse drug interaction [23]. This complexity not only prohibited inclusion of very old HF patients into randomized controlled trials but also hampers application of guidelines-recommended HF treatment in the real world. This was recently shown by the CHECK-HF registry where increasing age is associated with an incremental risk of non-prescription of recommended HF drug treatment [9,25]. Similar results were presented from a French survey focusing on HF treatment in very old chronic HF patients in follow-up by geriatric care centers [10] and likewise in octogenerians followed by the Euro Heart Failure survey II [26]. In concordance, not-receiving RAS inhibition, betablocker treatment, or MR antagonists was more likely in the $>$ 80 years stratum when compared with the 65–80 years stratum in the present study (RAS inhibition: 42.1 % vs. 25 %; betablockers: 42.5 % vs. 34.6 %; MRA: 89.2 % vs. 73.8 %).

In addition to not receiving a HF drug, underdosing remains the other key issue. Results from the BIOSTAT-HF trial including chronic stable HFrEF patients with a mean age of 67 years suggest that treatment with $<$ 50 % of the target dose of RAS inhibitors is associated with an increased incidence of the combined endpoint of mortality and HF hospitalization [27]. In accordance, a monocenter cohort including HHF patients with reduced LVEF and a mean age of 68 years showed that not being on a $\geq$ 50 % target dose level of RASi is associated with increased mortality [28]. In the present study, patients with a 1–25 % level of each pharmacological classes were older when compared to patients within the $>$ 25 % level, therefore, the present study provides further evidence that age is a risk factor for not receiving adequate HF drug dose treatment [9,10]. This raises the question whether low dose HF-drug treatment in the old has a beneficial effect when compared to not-receiving the drug.

The results of the present study indicate that low-dose RASi treatment when compared with no treatment is associated with a significant decrease of the incidence of the primary and the secondary endpoint independent of LVEF. This benefit is already significant at the 1–25 % level and as well at the $>$ 25 % target dose level. While this result is reassuring with respect to the care of the old HHF patient, the beneficial effect of low-dose ACEI on ACM is not new by itself since low-dose ACEI was already shown to reduce ACM as effectively as high-dose treatment in chronic stable HFrEF patients with a mean age of 64 years [29]. However, in contrast to the latter trial, the present study low-dose RASi also was related with reduction of the combined secondary endpoint. The status "on RASi" was also associated with an improved outcome in octogenarian patients of the Euro Heart Survey II, [26] and in propensity analyses of the EPICAL2-registry and the GREAT-Network [30,31]. In summary, there is concordant evidence from the present and previous studies indicating improved prognosis when RASi is applied in old HF patients and the present study provides new evidence that already a level of 1–25 % is beneficial.

However, betablocker treatment at the 1–25 % and $\geq$ 25 % level of target dose was not associated with a decrease of the incidence of the primary and secondary endpoint in the present study. This result is not different to results from the BIOSTAT-HF study where stable HFrEF patients $\geq$ 70 years had no benefit from betablocker treatment [27] while propensity-score matched analysis in HHF patients in follow-up by the GREAT Network suggests a benefit even in the very old HHF patient [30]. The latter result is concordant to efficacy of beta blocker treatment in the SENIORS trial including stable HFrEF and HFpEF patients with a mean age of 76 years. However, the beneficial effect of nebivolol was obtained in the context of a randomized controlled trial and patients had a mean maintenance dose of 77 % of the maximal target dose [18]. Therefore, absence of an effect of betablocker treatment in the present study population may relate to the low number of patients achieving a dose level corresponding to the maintenance dose in the SENIORS trial. On the other hand, results from the CIBIS-ELD study including HFrEF patients with a mean age of 72.9 years indicate that not the betablocker drug dose level but the decrease of heart rate is of clinical relevance in this age group of HF patients [17]. Altogether, the question whether dose or heart rate determine the prognostic effect of betablocker treatment remains controversial asking for further investigation.

Last not least, MRA treatment at the 1–25% level of target dose was associated with a decrease of the incidence of the secondary endpoint in this study population. While this result suffers from the overall low number of MRA-treated patients, it is nonetheless compatible with findings reported from the KCHF registry showing that MRA treatment reduced the endpoint combining ACM and rehospitalization while there was no significant association with ACM alone [2]. It remains unclear why the beneficial effect remains limited to the 1–25 % level of the target dose level but hyperkalemia may be an explanation as suggested from the results of a population-based study in the U.S. investigating the effect of spironolactone treatment [32].

5. Limitations

This observational study has a drawback related to its monocenter design, although study participants were treated in different departments (cardiology, internal medicine, geriatrics). Analysis of the treatment effect size on the basis of the percentage of target dose without considering the HF subtype may represent another potential confounder. Therefore, the multivariable analysis was adjusted by the MAGGIC score which accounts for the association between LVEF and mortality [12]. In addition, we performed a sensitivity analysis adjusting multivariable analysis with parameters of the present study population that were significantly related with 1-year ACM in univariable analysis, and LVEF was one of these parameters. Results of the MAGGIC-score adjusted multivariable analysis were considered reliable when the result of the sensitivity analysis corresponded suggesting robustness. Another limitation to this study is that maintenance of discharge drug prescription was not studied. This represents a confounder, however, the majority of primary or secondary endpoints occurred early, and results from the EPICAL-2 study and the Euro Heart Failure Survey 2 suggest that more than 80 % of HF drug prescription is maintained after discharge from HHF [26,30]. Furthermore, the large concordance of the association between the percentage target drug dose groups and the primary and secondary endpoints when analyzed as a function of the age stratum, can suggest that adherence to drug treatment was at least similar in both groups.

6. Conclusion

The most important finding of this study is that already RASi at the 1–25 % and likewise at the $>$ 25 % level of guidelines-recommended target dose decreases substantially the incidence of the primary and secondary endpoint in old patients with HHF. This observation should therefore motivate physicians in charge of these HHF patients to administer and, if possible, uptitrate heart failure drugs even in the old patient.

CRediT authorship contribution statement

Soborun N: data acquisition, Data curation, Writing – review & editing. **Müller M:** Formal analysis, Methodology, Writing – review & editing. **Abdurashidova T:** data acquisition, Data curation, Validation. **Tzimas G:** data acquisition, Writing – review & editing. **Schukraft S:**

Writing – review & editing, Validation. **Lu H:** Writing – review & editing, Validation. **Hugli O:** data acquisition, Writing – review & editing. **Vollenweider P:** Writing – review & editing. **Garnier A:** data acquisition. **Monney P:** data acquisition, Supervision, Validation, Writing – review & editing. **Hullin R:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Disclosure

No disclosures.

Data Availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.113615.

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