Title:

LONG-TERM CHANGES OF RENAL FUNCTION IN RELATION TO ACE INHIBITOR/ARB DOSING IN PATIENTS WITH HEART FAILURE AND CHRONIC KIDNEY DISEASE

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ABSTRACT

BACKGROUND: ACE-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have become cornerstones of therapy for chronic heart failure (CHF). Guidelines advise high target doses for ACEIs/ARBs, but fear of worsening renal function may limit dose titration in patients with concomitant chronic kidney disease (CKD).

METHODS: In this retrospective observational study, we identified 722 consecutive patients with systolic CHF, stable CKD stage III/IV (eGFR 15-60mL/min/1.73m²) and chronic ACEI/ARB treatment from the out-patient heart failure clinics at the Universities of Hull, UK and Heidelberg, Germany. Change of renal function, worsening CHF and hyperkalemia at 12 month follow-up were analyzed as a function of both baseline ACEI/ARB dose and dose-change from baseline.

RESULTS: ΔeGFR was not related to baseline dose of ACEI/ARB (P=0.58), nor to relative (P=0.18) or absolute change of ACEI/ARB dose (P=0.21) during follow-up. Expressing change of renal function as a categorical variable (improved/stable/decreased) as well as subgroup analyses with respect to age, sex, NYHA, left ventricular ejection fraction, diabetes, concomitant aldosterone antagonists, CKD-stage, hypertension, ACEI vs. ARB, and congestion status yielded similar results. There was no association of dose/dose-change with incidence of either worsening CHF or hyperkalemia.

CONCLUSIONS: In patients with systolic CHF and stable CKD stage III/IV, neither continuation of high doses of ACEI/ARB nor up-titration were related to adverse changes in longer-term renal function. Conversely, down-titration was not associated with improvement in eGFR. Use of high doses of ACEI/ARB and their up-titration in patients with CHF and CKD III/IV may be appropriate provided the patient is adequately monitored.

Words: 249

INTRODUCTION

In patients with chronic systolic heart failure (CHF), concomitant chronic kidney disease (CKD) is common and conveys a poor prognosis (1-4). Blockade of the renin-angiotensin-system (RAS) with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has been a guideline recommended cornerstone for the management of both CKD and CHF for the last 25 years (4-7).

As impaired renal function may adversely affect metabolism and elimination of ACEIs/ARBs (8-11), trials of CHF generally excluded patients with severe CKD. Thus, surprisingly little is known about how to manage patients suffering from both CHF and CKD (12). International guidelines for CHF advise high target doses of ACEIs/ARBs in order to reduce CHF morbidity and mortality (13). Higher doses of RAS-blockade, on the other hand, may be associated with higher rates of renal complications in patients with CHF (14, 15). In contrast, guidelines for renal disease do not specify target doses of ACEIs/ARBs (16). Then again, there is a general recommendation that lower doses should be used in patients with CKD to prevent hyperkalemia and acute renal failure (8-11).

ACEIs/ARBs cause constriction of the post-glomerular efferent arteriole, and current evidence supports their use for renal protection particularly in patients with diabetes and/ or hypertension (16, 17, 24). Here, CKD is caused by sclerosis of the glomeruli, and ACEIs/ARBs improve renal function by lowering glomerular pressure (9-11). In CHF patients in contrast, renal venous congestion and a fall in the trans-renal pressure gradient mainly contribute to the development and progression of CKD (1). Thus, ACEIs/ARBs may have differential effects on renal function depending on the underlying pathophysiology of CKD.

There are no clinical trials randomizing different ACEI/ARB doses to patients with either CKD alone or as a complication of CHF. The optimal dosing strategy in these patients for renal protection or for safety endpoints such as worsening CHF and hyperkalemia is unknown. We therefore sought to explore the association of baseline dose and subsequent dose titration of ACEIs/ARBs with renal function, worsening CHF and hyperkalemia in a retrospective cohort of CHF out-patients with reduced ejection fraction and CKD stage III/IV.

METHODS

PATIENT SELECTION

We retrospectively identified 722 consecutive patients with stable CHF due to chronic systolic dysfunction and concomitant stable CKD stage III/IV who attended the community heart failure clinics of the Department of Academic Cardiology, University of Hull, UK, or the University Hospital Heidelberg, Germany, between May 1995 and March 2012 who met the following inclusion criteria:

1. A diagnosis of CHF based on relevant symptoms and signs supported by objective evidence of substantial abnormalities of cardiac function on imaging or invasive hemodynamics (13).
2. Systolic dysfunction defined as a left ventricular ejection fraction (LVEF) <45%.
3. Assessment of renal function both at baseline and at 12 months follow-up.
4. CKD was defined according to the KDIGO practice guidelines (16) as a low glomerular filtration rate (GFR) present for at least 3 months. All patients suffered from either stage III or stage IV CKD at baseline. Stage III CKD was defined as a GFR of 30 – 60 mL/min/1,73m², while stage IV CKD was defined as a GFR of 15 – 29 mL/min/1,73m² (17). The GFR was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation. Performance accuracy of the MDRD formula for estimation of GFR was shown to be highly accurate in patients with GFR <60 mL/min/1,73m² (18).
5. Stable medication with ACEIs or ARBs for at least 1 month prior to inclusion.

And none of the exclusion criteria:

1. Cardiac decompensation requiring inotropic support in the previous 3 months.
2. A history of primary or severe concomitant valve disease.
3. Requirement of renal replacement therapy.
4. Estimated GFR (eGFR) <15 mL/min/1.73m² at baseline.

Medication was at the discretion of the referring physician with respect to guideline recommended drugs. Target doses and dose equivalents for ACEIs and ARBs were derived from ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (13). For example, daily doses of 10 mg

ramipril or 32 mg candesartan were both considered as 100% dose equivalent, while 5 mg ramipril and 16 mg candesartan were defined as 50% dose equivalent.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committees. All patients gave their written informed consent for their data to be recorded and used for research purposes. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

FOLLOW-UP AND ENDPOINTS

Patient follow-up was by scheduled visits to the respective outpatients' clinics. The predefined primary endpoint for the purpose of this study was the change of renal function as defined by the change in eGFR at 12 months' follow-up. Secondary/safety endpoints were hospitalization due to worsening CHF and significant hyperkalemia (serum potassium >5.5 mmol/L) between visits. The follow-up visit for the primary purpose of the present analysis occurred at 365 (353-377) days. The frequency of additional interim follow-up visits and follow-up blood samples were at the discretion of the responsible physician with respect to guideline recommendations and the patients' individual risk factors for worsening renal function and/or hyperkalemia. Medication was recorded and serum creatinine levels measured at each visit.

Secondary endpoint status was determined at the follow-up visit and verified either through electronic hospital records or telephone calls to the patients' physicians.

In order to ensure that all included patients were on ACEI/ARB treatment for at least 4 weeks at the time of study inclusion the baseline visit was defined as the (at least) second consecutive visit to the heart failure outpatient department that reported ACEI/ARB treatment AND offered complete information on ACEI/ARB dosing, eGFR, hospitalization due to worsening CHF, and serum potassium measurements.

SUBGROUPS

All analyses were repeated in pre-specified subgroups with respect to age (≤median vs. >median), sex (male vs. female), NYHA functional class (I/ II vs. III/ IV), LVEF (≤35% vs. >35%) diabetes (yes vs. no), concomitant therapy with aldosterone antagonists (MRA) (yes vs. no), stage of CKD (stage IV: eGRF 15-29 mL/min/1.73m² vs. stage III: eGFR 30-59 mL/min/1.73m²), hypertension (yes vs. no), type of RAS blockade (ACEI vs. ARB), and admission for worsening CHF between visits (yes vs. no).

STATISTICS

Descriptive statistics and comparative statistics were obtained using MedCalc software version 12.7 (Ostend, Belgium). Results are displayed using GraphPad Prism version 6.02 for Windows (La Jolla, California, USA). All tests are two-tailed and an arbitrary *P* value of less than 5% was regarded as statistically significant. The data are presented as mean ± SD, median [interquartile range], or number (%) as appropriate. To compare frequencies and 12 months hospitalization rates, chi-squared analysis was performed. To test for significant differences between two groups, the two-sample Wilcoxon test and Student's t test were used where appropriate. To test for significant differences between more than two groups, the Kruskal-Wallis test and analyses of variance (ANOVA) were used.

In order to analyze the association of ACEI/ARB dose equivalents at baseline and renal function, different strategies were applied: ACEI/ARB dose equivalents were entered into the analyses both as a continuous variable and as a categorical variable – stratified in 3 groups as follows: low-dose: ≤33%, moderate-dose: 34-66%, and high-dose: >66% of the maximum recommended dose equivalent from CHF guidelines (13).

We analyzed mean change in eGFR at 12 months with respect to baseline ACEI/ARB dose equivalents and changes of these dose equivalents from baseline. When analyzing the ACEI/ARB dose equivalent as a categorical variable, down-titration was defined as a reduction of ACEI/ARB dose equivalent to a different dose group. Similarly, up-titration was defined as an increase of ACEI/ARB dose equivalent to a different dose group. Furthermore, we compared ACEI/ARB dosing between patients who experienced a pre-specified alteration of renal function in absolute values (ΔeGFR >±

10mL/min/1.73m² vs. ΔeGFR ≤±10 mL/min/1.73m²) or relative values (ΔeGFR >±10% vs. ΔeGFR ≤±10%).

When treating ACEI/ARB dosing as a continuous variable, linear regression analyses were performed to evaluate the relation between ACEI/ARB dosing and eGFR. These included ACEI/ARB dose equivalents at baseline, absolute changes of ACEI/ARB dose equivalents, and relative changes of ACEI/ARB dose equivalents together with absolute changes of eGFR and relative changes of eGFR.

RESULTS

BASELINE CHARACTERISTICS

A total of 722 patients was included, 341 (47%) from Hull and 381 (53%) from Heidelberg. Of these, 148 patients (20.5%) received low-dose, 235 patients (32.5%) moderate-dose, and 339 patients (47.0%) high-dose ACEI/ARB at baseline.

Age, mean eGFR and serum potassium concentrations were similar in each dose group (*Table 1).* Although LVEF was higher in patients with low-dose ACEI/ARB treatment, NTproBNP levels were higher and 6 minute walk test distance was shorter.

Over 12 months of follow-up, mean eGFR was stable in the overall population (ΔeGFR 0.51 (-7.06 – 8.57 ml/min/1.73m²)), and 140 (19%), 439 (61%) and 143 (20%) patients had doses of ACEI/ARBs reduced, maintained or increased.

Table 1: Baseline characteristics with respect to ACEI/ARB dose equivalents

	All patients (n = 722)	**Low-dose (n = 148)**	**Moderate-dose (n = 235)**	**High-dose (n = 339)**	***P* value**
Men (n, %)	493 (68)	85 (57)	161 (68)	247 (73)	*0.003*
Age (years)	69 ± 11	69 ± 13	69 ± 10	69 ± 11	0.93
Diabetes (n, %)	206 (30)	37 (26)	62 (27)	107 (33)	0.23

Table 1: Baseline characteristics with respect to ACEI/ARB dose equivalents

Hypertension (n, %)	424 (59)	80 (54)	131 (56)	213 (63)	0.10
COPD (n, %)	133 (18)	25 (17)	51 (22)	57 (17)	0.29
NYHA (n, %)					0.13
I	87 (12)	13 (9)	23 (10)	51 (15)	
II	329 (46)	62 (42)	103 (44)	164 (49)	
III	289 (40)	69 (47)	103 (44)	117 (35)	
IV	11 (2)	4 (3)	3 (1)	4 (1)	
BMI (kg/m²)	28.0 ± 5.2	27.2 ± 5.2	27.5 ± 5.0	28.6 ± 5.3	*0.006*
SBP (mmHg)	121 ± 24	122 ± 27	119 ± 23	122 ± 23	0.20
DBP (mmHg)	72 ± 13	71 ± 14	72 ± 12	73 ± 13	0.28
HR (1/min)	72 ± 15	74 ± 14	72 ± 15	71 ± 15	0.11
LVEF (n, %)	32 ± 12	34 ± 12	30 ± 12	32 ± 12	*0.009*
LVEDD (mm)	34 ± 27	26 ± 25	38 ± 28	35 ± 26	*<0.001*
6 MWT (m)	360 ± 141	314 ± 144	353 ± 141	382 ± 136	*<0.001*
eGFR (mL/min/1.73m²)	47 ± 10	46 ± 11	47 ± 10	48 ± 9	*0.01*
Sodium (mmol/L)	139 ± 3	138 ± 3	139 ± 3	139 ± 3	0.09
Potassium (mmol/L)	5 ± 1	5 ± 3	5 ± 1	5 ± 1	0.68
Urea (mmol/L)	6.8 ± 5.7	5.8 ± 6.0	7.3 ± 5.7	6.8 ± 5.5	*0.05*
NTproBNP (pmol/L)	186 (77-444)	257 (90-609)	246 (82-480)	150 (73-361)	*0.002*
ACEI (n, %)	559 (77)	94 (64)	171 (73)	294 (87)	*<0.001*
ARB (n, %)	163 (23)	54 (36)	64 (27)	45 (13)	*<0.001*
Beta blocker (n, %)	567 (79)	106 (72)	188 (80)	273 (81)	0.07
Beta blocker dose equivalent* (n, %)	50 (25-100)	25 (19-50)	50 (25-95)	50 (38-100)	*<0.001*

Table 1: Baseline characteristics with respect to ACEI/ARB dose equivalents

MRA (n, %)	352 (49)	66 (45)	109 (46)	177 (52)	0.50
Digitalis (n, %)	180 (25)	38 (26)	62 (26)	80 (24)	0.73
Loop diuretic (n, %)	590 (82)	126 (85)	185 (79)	279 (82)	0.73
Loop diuretic (mg furosemide)	60 (40-80)	40 (40-80)	60 (40-80)	80 (40-80)	0.60
Aspirin (n, %)	157 (22)	35 (24)	45 (19)	77 (23)	0.49
Warfarin (n, %)	372 (52)	62 (42)	128 (54)	182 (54)	*0.03*
Statin (n, %)	434 (60)	77 (52)	144 (61)	213 (63)	0.07
Allopurinol (n, %)	120 (17)	16 (11)	40 (17)	64 (19)	0.09

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association functional class; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; LVEDD, left ventricular enddiastolic diameter; 6 MWT, 6 minute walk test; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; MRA, mineralocorticoid receptor antagonist. *Beta blocker dose equivalents were derived from ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (13). For example, daily doses of 10 mg bisoprolol or 50 mg carvedilol were both considered as 100% dose equivalent

CHANGE OF eGFR AS A FUNCTION OF ACEI/ARB DOSE EQUIVALENTS

There was no difference in the mean change of eGFR at 12 months amongst the three baseline ACEI/ARB dose groups. Neither up-titration, maintenance of the same dose, nor down-titration of ACEI/ARBs was associated with change in eGFR at 12 months (*Figure 1).*

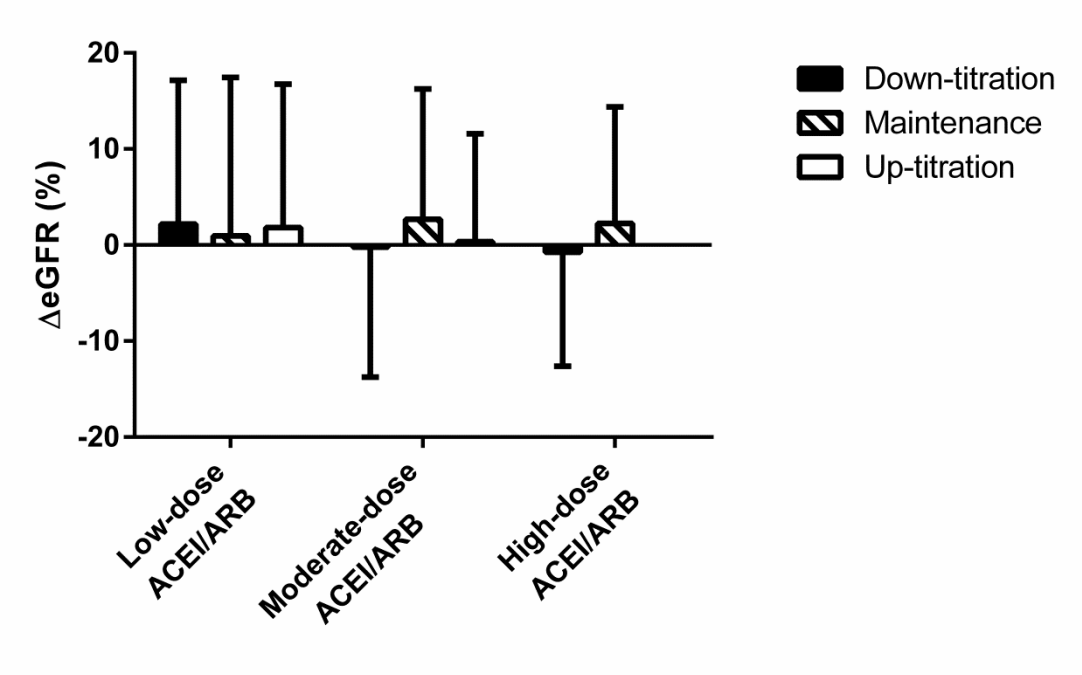

Figure 1: Change of eGRF as a function of ACEI/ARB dose equivalents at baseline and subsequent dose changes.

eGFR, estimated glomerular filtration rate using the Modification of Diet in renal Disease equation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Linear regression analyses showed no relationship between either change in eGFR and ACEI/ARB dose equivalents at baseline or change in eGFR and change in ACEI/ARB dose equivalents (*Table 2, Figures 2 a) and b*)).

Table 2: Regression analyses of change in renal function as a function of ACEI/ARB dosing in the complete sample

	ACEI/ARB dose equivalent at baseline		**ΔACEI/ARB dose equivalent (abs.)**	
	Beta	***P* value**	**Beta**	***P* value**
ΔeGFR (abs.)	0.04	0.26	0.04	0.21
ΔeGFR (%)	0.02	0.58	0.04	0.21

eGFR, estimated glomerular filtration rate using the Modification of Diet in renal Disease equation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

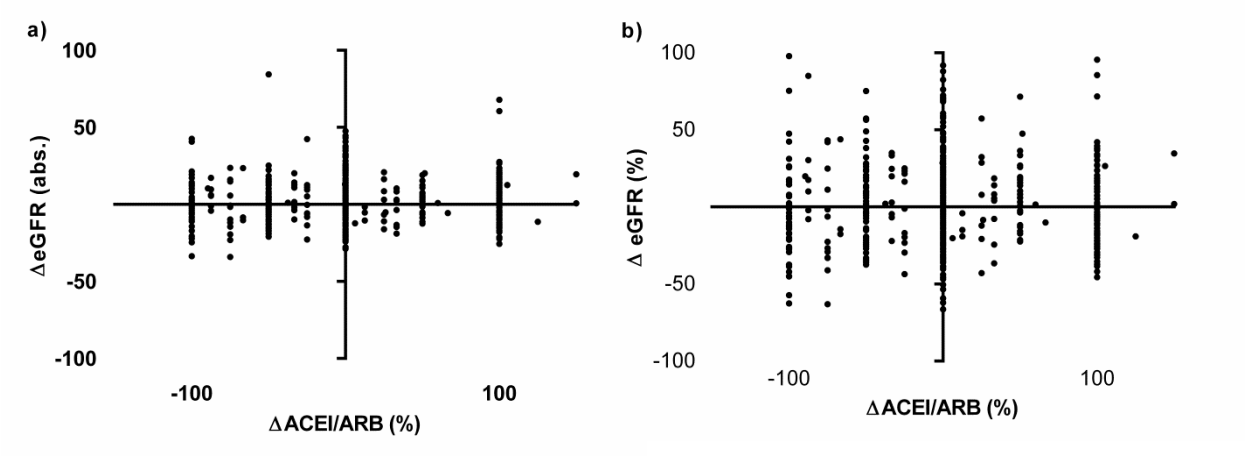

Figure 2: Relationship between a) absolute change in eGFR and relative change in ACEI/ARB dose equivalents; b) relative change in eGFR and relative change in ACEI/ARB dose equivalents.

eGFR, estimated glomerular filtration rate using the Modification of Diet in renal Disease equation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

CHANGE OF eGFR AS A FUNCTION OF PREDEFINES CHANGES OF eGFR

The proportion of patients who experienced a change in eGFR was similar between baseline dose groups, expressed either in absolute terms or as change relative to baseline, irrespective of subsequent change in ACEI/ARB dose ($P = 0.65$) (*Tables 3 and 4).*

Table 3: Number of patients with a pre-specified alteration of eGFR (absolute values) as a function of ACEI/ARB dosing strategy

ACEI/ARB dose at baseline	**ACEI/ARB dose after 12 months**	**ΔeGFR after 12 months (%)**		
		Decrease >10 mL/min/1.73m²	**Stable (≤ ± 10 mL/min/1.73m²)**	**Increase >10 mL/min/1.73m²**
Low-dose (n = 148)	Withdrawal (n = 20)	5 (25)	8 (40)	7 (35)
	Maintenance (n = 63)	14 (22)	36 (57)	13 (21)
	Up-titration (n = 65)	11 (17)	37 (57)	17 (26)
Moderate-dose (n = 235)	Down-titration (n = 48)	9 (19)	28 (58)	11 (23)
	Maintenance (n = 109)	15 (14)	69 (63)	25 (23)
	Up-titration (n = 78)	16 (21)	46 (59)	16 (21)
High-dose (n = 339)	Down-titration (n = 72)	17 (24)	40 (56)	15 (21)
	Maintenance (n = 267)	37 (14)	172 (64)	58 (22)
n		124	436	162

ACEI, angiontensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; n, number of patients.

Table 4: Number of patients with a pre-specified alteration of eGFR (relative/% values) as a function of ACEI/ARB dosing strategy

ACEI/ARB dose at baseline	ACEI/ARB dose after 12 months	ΔeGFR after 12 months (%)		
		Decrease >10%	Stable (≤ ± 10%)	Increase >10%
Low-dose (n = 148)	Withdrawal (n = 20)	6 (30)	5 (25)	9 (45)
	Maintenance (n = 63)	25 (40)	16 (25)	22 (35)
	Up-titration (n = 65)	25 (38)	20 (31)	20 (31)
Moderate-dose (n = 235)	Down-titration (n = 48)	20 (42)	12 (25)	16 (33)
	Maintenance (n = 109)	33 (30)	38 (35)	38 (35)
	Up-titration (n = 78)	26 (33)	25 (32)	27 (35)
High-dose (n = 339)	Down-titration (n = 72)	24 (33)	26 (36)	22 (31)
	Maintenance (n = 267)	72 (27)	94 (35)	101 (38)
n		231	236	255

ACEI, angiontensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; n, number of patients.

SUBGROUPS

We did not find any relation between renal function and ACEI/ARB dose in any of the pre-specified subgroups (*Tables 5 and 6*).

Table 5: Linear regression analyses of absolute change of eGFR (dependent variable) as a function of ACEI/ARB dosing strategy in pre-specified subgroups

Subgroup		ACEI/ARB dose at baseline		ΔACEI/ARB dose (abs.)		ΔACEI/ARB dose (%)	
		Beta	***P*-value**	**Beta**	***P*-value**	**Beta**	***P*-value**
Age	≤median	-0.06	0.28	0.06	0.35	0.01	0.90
	>median	0.08	0.09	-0.02	0.75	0.03	0.56
Sex	male	0.01	0.83	0.04	0.40	0.01	0.86
	female	0.03	0.63	-0.01	0.83	0.02	0.74
NYHA	I/ II	0.03	0.56	0.07	0.19	0.07	0.14
	III/ IV	0.01	0.89	-0.04	0.52	-0.06	0.30
LVEF	≤35%	-0.01	0.80	-0.01	0.81	-0.04	0.41
	>35%	0.01	0.86	0.08	0.27	0.08	0.29
Diabetes	yes	0.11	0.11	-0.07	0.35	-0.01	0.92
	no	-0.01	0.80	0.05	0.31	0.03	0.56
MRA	yes	-0.02	0.72	0.06	0.28	0.03	0.64
	no	0.05	0.30	-0.01	0.85	0.02	0.73
CKD	stage III	0.05	0.17	0.02	0.60	0.01	0.86
	stage IV	-0.12	0.41	0.05	0.74	0.03	0.85
RR ↑	yes	0.03	0.61	0.09	0.11	0.06	0.31
	no	0.00	0.99	-0.06	0.27	-0.02	0.72
RAS blockade	ACEI	0.00	0.94	-0.00	0.96	-0.04	0.40
	ARB	0.09	0.24	0.10	0.24	0.12	0.14
Worsening CHF	yes	0.08	0.45	0.21	0.06	0.16	0.14
	no	-0.01	0.91	-0.01	0.75	-0.00	0.99

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; CKD, chronic kidney disease; RR↑, hypertension; RAS, renin angiotensin system.

Table 6: Linear regression analyses of relative (%) change of eGFR (dependent variable) as a function of ACEI/ARB dosing strategy in pre-specified subgroups

Subgroup		**ACEI/ARB dose at baseline**		**ΔACEI/ARB dose (abs.)**		**ΔACEI/ARB dose (%)**	
		Beta	***P*-value**	**Beta**	***P*-value**	**Beta**	***P*-value**
Age	≤median	-0.10	0.09	0.05	0.41	0.04	0.45
	>median	0.08	0.13	-0.02	0.73	0.04	0.49
Sex	male	0.00	0.93	0.02	0.73	0.01	0.91
	female	-0.01	0.86	0.02	0.83	0.05	0.44
NYHA	I/ II	0.03	0.54	0.05	0.32	0.08	0.11
	III/ IV	-0.03	0.60	-0.01	0.83	-0.01	0.92
LVEF	≤35%	-0.03	0.57	-0.02	0.65	-0.05	0.39
	>35%	-0.03	0.65	0.11	0.13	0.17	0.02
Diabetes	yes	0.10	0.17	-0.03	0.68	0.01	0.90
	no	-0.04	0.42	0.03	0.52	0.05	0.29
MRA	yes	-0.04	0.48	0.05	0.42	0.06	0.31
	no	0.03	0.58	-0.00	0.95	0.04	0.46
CKD	stage III	0.05	0.17	0.01	0.73	0.01	0.77
	stage IV	-0.10	0.46	0.08	0.59	0.09	0.54
RR↑	yes	0.02	0.70	0.07	0.23	0.06	0.26
	no	-0.04	0.50	-0.03	0.58	0.02	0.75

RAS	ACEI	-0.01	0.79	-0.02	0.70	-0.04	0.36
blockade	ARB	0.03	0.74	0.14	0.09	0.19	0.02
Worsening	yes	0.07	0.51	0.20	0.07	0.18	0.11
CHF	no	-0.03	0.51	-0.01	0.82	0.02	0.59

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; CKD, chronic kidney disease; RR↑, hypertension; RAS, renin angiotensin system.

SECONDARY/SAFETY ENDPOINTS

Of 722 patients included into this study, 90 patients (12%) were hospitalized due to worsening CHF throughout the period considered. Of these, 23 patients (3%) decompensated at least twice. Hospitalization rates were higher in patients with CKD stage IV as compared to those in CKD stage IIIa and IIIb ($P = 0.02$). There was no relation between ACEI/ARB equivalent dose at baseline and hospitalization due to worsening CHF ($P = 0.27$). However, hospitalization rates differed with respect to changes of ACEI/ARB dose equivalents (*Table 7*). When considering both stage of CKD (stage IIIa vs. stage IIIb vs. stage IV) and ACEI/ARB dose equivalent at baseline (low-dose vs. moderate-dose vs. high-dose), patients with CKD stage IV and moderate-dose ACEI/ARB therapy at baseline (n = 17) had the highest hospitalization rate (n = 6). These data, however, should be interpreted with caution due to small numbers.

Table 7: Hospitalization due to worsening CHF as a function of ACEI/ARB dosing strategy

ACEI/ARB dose at baseline	**ACEI/ARB dose after 12 months**	**No hospitalization (n, %)**	**Hospitalization (n, %)**	***P*-value**
Low-dose (n = 148)	Withdrawal (n = 20)	17 (85)	3 (15)	
	Maintenance (n = 63)	50 (79)	13 (21)	
	Up-titration (n = 65)	57 (88)	8 (12)	
Moderate-dose	Down-titration (n = 48)	40 (83)	8 (17)	0.04

(n = 235)	Maintenance (n = 109)	93 (85)	16 (15)
	Up-titration (n = 78)	73 (94)	5 (6)
High-dose	Down-titration (n = 72)	58 (81)	14 (19)
(n = 339)	Maintenance (n = 267)	244 (91)	23 (9)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; n, number of patients.

During the 12 months observation period, severe hyperkalemia occurred in 24 patients (3%). In 3 patients, serum potassium levels greater than 5.5 mmol/L were detected twice. There was no relation between incidence of hyperkalemia and stage of CKD ($P = 0.12$), incidence of hyperkalemia and baseline ACEI/ARB dose equivalent ($P = 0.52$), or incidence of hyperkalemia and change of ACEI/ARB dose equivalent ($P = 0.88$).

DISCUSSION

In this large, international sample of systolic CHF out-patients with concomitant stable CKD stage III/IV, we investigated the association of ACEI/ARB dosing and long-term renal function. Our main findings are that, on average:

- Dose of ACEIs/ARBs is not associated with severity of renal dysfunction at baseline or at one year follow-up.
- Up-titration from lower doses of ACEI/ARB is not associated with deterioration in renal function.
- Conversely, down-titration from higher doses of ACEI/ARB is not associated with improved renal function at one year.
- These results were consistent across subgroups by age, sex, NYHA functional class, LVEF, diabetes, concomitant MRA therapy, stage of CKD, hypertension, and worsening CHF during the observation period.

- There was no association between baseline ACEI/ARB dose and the occurrence of hyperkalemia or worsening CHF during 12 months follow-up.

Even though renal dysfunction is common in CHF, patients with severe concomitant CKD have been excluded from many trials investigating RAS blockade in CHF. This leaves the clinician caring for patients with CHF and CKD with a certain difficulty regarding individual dosing of ACEIs/ARBs. Although subgroup analyses of CHF trials and retrospective registry data suggest that ACEI/ARB therapy may improve prognosis in patients with CHF and concomitant CKD (3-7, 19), little is known about the effects of ACEI/ARB therapy on renal function in these patients (12, 20).

In fact, the respective guidelines for the management of CHF and CKD provide the clinician with a paradox: While renal guidelines recommend not to discontinue ACEIs/ARBs in patients with an eGFR <30 mL/min/1.73m² (16, 17), CHF guidelines advise that ACEI/ARBs should only be initiated when eGFR is above 30 mL/min/1.73m² and be stopped if it falls below 20 mL/min/1.73m² (13). This may account for the lower utilization of ACEIs/ARBs in clinical practice as eGFR declines (3, 6).

Our data support the "nephrological" approach to using of ACEIs/ARBs in patients with CKD stage IV rather than concerns from CHF cohorts that use of ACEIs/ARBs might precipitate acute renal failure (21, 22). There are surprisingly little data against which to compare our study. De Vecchis et al. (23) compared 15 patients on high-dose ACEI treatment with 42 on low-dose. They reported that the use of high ACEI/ARB doses predicted acute renal failure. In extension, de Silva et al. showed in 72 patients with CHF and concomitant renal dysfunction that only one fifth of patients experienced a substantial recovery of renal function following ACEI down-titration (12).

It is here that our study significantly expands current evidence. Not only did we demonstrate the absence of any long-term adverse association of high-dose ACEI/ARB therapy with renal function in a substantially larger cohort - we were further able to show that up-titration to guideline recommended higher target doses was not associated with an adverse effect on long-term renal function, too. The fact that this was observed in all pre-specified subgroups further corroborates our findings. In addition, we found no association between baseline ACEI/ARB dose and the occurrence of hyperkalemia or worsening CHF during 12 months follow-up. This is important for clinical practice as our data argues

against withholding ACEI/ARB treatment from CHF patients in advanced CKD on grounds of fear of adverse effects on renal function or hyperkalemia.

A review of 12 randomized clinical trials of ACEIs in hypertensive and/or diabetic patients with renal dysfunction (serum creatinine >1.4 mg/dL [123.9 µmol/L]) indirectly supports this notion further (24). It found that an acute increase in serum creatinine of up to 30% that stabilized within the first two months of ACEI therapy strongly predicted long-term preservation of renal function.

At last, we found no evidence of a dose-dependent adverse relationship between ACEI/ARB treatment and renal function. From our data, we speculate that dose-reduction of ACEIs/ARBs from high doses does not appear to improve eGFR in patients with stable renal dysfunction. This again is of great clinical importance as it means that dose reduction should not be performed based on eGFR only – arguing against a common practice encountered in daily care for these patients.

LIMITATIONS

A potential limitation of the present study is its observational design. We cannot claim cause and effect but merely describe associations. In some cases, ACEI/ARB dose was down-titrated and this may have been clinically appropriate for these patients. We cannot comment on possible transient GFR changes, nor can we comment on reasons for ACEI/ARB titration. There was, however, no systematic relationship between baseline eGFR, ACEI/ARB dosing and long-term renal function. In addition, our data are derived from comprehensive out-patient data-bases with close surveillance. These data therefore reflect the effect of ACEI/ARB therapy in real-world patients in contrast to those selected for randomized trials. This adds to the relevance of our results as differences between study cohorts and real world patients are very common and there are no randomized trials examining these issues so far.

As the aim of this study was to investigate the relationship between ACEI/ARB dosing and long-term renal function, we only included patients who survived for at least 12 months. Thus, owing to the study design, we cannot comment on mortality in this study. Literature, however, provides good evidence that RAS blockade reduces mortality in CHF with concomitant CKD (3-7, 19).

Our analysis was restricted to patients who were on stable ACEIs/ARBs for at least one month prior to study inclusion. Thus, study results may not be transferred to patients with new onset ACEI/ARB treatment. In addition, we only included patients with systolic CHF, as heart failure with preserved ejection fraction represents a heterogeneous disease that subsumes different etiologies and different pathophysiological mechanisms. The long span of patient enrolment in our study covers a period with important changes of recommended CHF management. Most importantly, the number of patients with concomitant MRA treatment increased, which may adversely affect renal function when added to ACEI/ARBs. However, our subgroup analyses showed no relationship between renal function and ACEI/ARB dosing irrespective of concomitant MRA therapy.

In contrast to data from population based studies (25, 26), the prevalence of significant hyperkalemia was very low in our study. While previous studies identified age, stage of CKD and RAS blocking medication as predictors of hyperkalemia in patients with CHF (25-27), we found no relationship between the incidence of hyperkalemia and stage of CKD or ACEI/ ARB treatment. However, our results correspond well to data from randomized ACEI trials who observed hyperkalemia in less than 2% of patients (24). It is possible that the quality of care these patients received contributed to the apparent safety of using higher doses of ACEI/ARBs in the present study. Moreover, the inclusion of patients who were on stable ACEIs/ARBs for at least one month may have resulted in a pre-selection of patients who tolerate ACEIs/ARBs. However, in everyday clinical practice, worsening renal function or hyperkalemia usually lead to a pause in ACEI/ARB treatment instead of a permanent stop of therapy. Therefore, patients with prior complications due to ACEI/ARB treatment may still have been included into the present study.

There is on-going discussion in non-CHF cohorts, whether reducing albuminuria and blood pressure should be used as surrogates to estimate the efficacy of renal protection with RAAS inhibitors.(28, 29) As we did not measure proteinuria, we cannot comment on this. On the other hand, change in serum creatinine is an accepted marker for change in renal function (30, 31). Lastly, as patients included in our analysis were mainly white Caucasians, applying the results obtained from our study to other populations from different ethnic/racial background may not be reliable.

CONCLUSIONS

In stable out-patients with CHF and CKD stage III/ IV, neither high-dose ACEI/ARB therapy, nor up-titration to high-dose equivalents was associated with adverse long-term changes in renal function. There were no safety concerns to this strategy. Down-titration from high doses, on the other hand, was not related to an improvement in renal function. In patients with stable CHF and CKD, up-titration of ACEIs/ARBs may therefore be considered even in the presence of moderate to severe renal impairment. Until more evidence is acquired, this strategy should be pursued only when patients are managed by a system of care that ensures regular checks of renal function and potassium.

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