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Associations of albuminuria in patients with chronic heart failure: findings in the ALiskiren Observation of heart Failure Treatment study

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Aims To examine the relationships between baseline characteristics and urinary albumin excretion in the extensively phenotyped patients in the ALiskiren Observation of heart Failure Treatment (ALOFT) study.

Methods and results Urinary albumin creatinine ratio (UACR) was available in 190 of 302 (63%) patients randomized in ALOFT. Of these, 107 (56%) had normal albumin excretion, 63 (33%) microalbuminuria, and 20 (11%) macroalbuminuria. Compared with patients with normoalbuminuria, those with microalbuminuria had a greater prevalence of diabetes (48 vs. 26%, $P = 0.005$) and a lower estimated glomerular filtration rate (eGFR) (60.7 vs. 68.3 mL/min/1.73 m^2, $P = 0.01$). Patients with macroalbuminuria had additional differences from those with a normal UACR, including younger age (63 vs. 69 years, $P = 0.02$), higher glycated haemoglobin (HbA1c; 7.9 vs. 6.2%, $P < 0.001$), and different echocardiographic findings. Of the non-diabetic patients, 28% had microalbuminuria and 7% had macroalbuminuria. Independent predictors of UACR in these patients included N-terminal pro B-type natriuretic peptide (NT-proBNP), HbA1c, and left ventricular diastolic dimension. Increased UACR was not associated with markers of inflammation or of renin angiotensin aldosterone system activation and was not reduced by aliskiren.

Conclusions Increased UACR is common in patients with heart failure, including non-diabetics. Urinary albumin creatinine ratio is independently associated with HbA1c and NT-proBNP, even in non-diabetic patients.
Clinical Trial Registration: ClinicalTrials.gov NCT00219011

Keywords Heart failure • Albuminuria • Kidney • Proteins

Introduction

The prevalence and prognostic significance of increased urinary albumin excretion in patients with chronic heart failure was recently reported in two large studies.[1,2] Microalbuminuria was present in between 20 and 30% of patients (and macroalbuminuria in 5 and 11%) and was common even in the absence of diabetes, hypertension, and renal dysfunction. An elevated urinary albumin creatinine ratio (UACR) was associated with a significantly increased risk of adverse clinical outcomes, including death, even after adjustment for other prognostic variables.[1,2]

The pathophysiological mechanisms underlying albuminuria in heart failure are unknown. However, several systemic disease processes that occur in patients with heart failure have been linked to elevated urinary albumin excretion, including diffuse vascular dysfunction, systemic inflammation, and neurohumoral activation.[3–5]

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In heart failure, cardio-renal interactions lead to several abnormalities of renal function, including reduction in renal arterial flow, increased renal venous pressure, and tubular dysfunction.[6–10] The former two abnormalities may alter glomerular haemodynamics and permeability.[3–5]

We studied urinary albumin excretion in patients with heart failure enrolled in the ALiskiren Observation of heart Failure Treatment (ALOFT) study.[11] These participants were extensively phenotyped, permitting detailed comparison of the characteristics of those with and without an elevated UACR and identification of potential pathophysiological correlates of increased urinary albumin excretion in heart failure.

Methods

The design and principal findings of the ALOFT study have been described elsewhere.[11] Briefly, 302 patients with New York Heart Association (NYHA) class II–IV heart failure, current or past history of hypertension, and plasma B-type natriuretic peptide (BNP) >100 pg/mL who had been treated with either an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and a beta-blocker were randomized to either treatment with the renin inhibitor aliskiren or placebo.

Patients with reduced and preserved left ventricular ejection fraction (LVEF) were included. Patients were excluded if they met any of the following criteria: treatment with both an ACE inhibitor and ARB (combination of either with an aldosterone antagonist was permitted); heart failure related to obstructive valve disease, hypertrophic, restrictive or infective cardiomyopathy, pregnancy, or lung disease; systolic blood pressure <90 mmHg; serum potassium of 5.1 mmol/L or higher; creatinine >2.0 mg/dL (177 μmol/L), history of dialysis or nephrotic syndrome; myocardial infarction, cerebrovascular accident or transient ischaemic attack, or coronary revascularization within 6 months; cardiac resynchronization device or implantable cardioverter defibrillator; and prior malignancy or other diseases likely to greatly limit life expectancy, adherence to the protocol, or absorption of study drug. The study consisted of two phases: a 2-week single-blind placebo run-in (to assess eligibility, particularly BNP concentration, and patient adherence to study drug) and a 12-week randomized, double-blind, parallel group, phase in which patients received either placebo or aliskiren 150 mg once daily in an equal ratio. Patients were evaluated at 2, 4, 8, and 12 weeks after randomization. Blood chemistry was checked at each of these time points.

The primary objective of the ALOFT study was to assess the tolerability and safety of aliskiren, specifically the incidence of renal dysfunction, symptomatic hypotension, and hyperkalaemia (potassium >5.5 mmol/L).

The key secondary efficacy assessments included evaluation of the effect of aliskiren, compared with placebo, on N-terminal pro B-type natriuretic peptide (NT-proBNP), BNP, aldosterone, signs and symptoms of heart failure (and NYHA class), echocardiographic measures of cardiac size and ventricular function, blood pressure, heart rate variability, and other markers of autonomic function measured from an ambulatory electrocardiogram recording, quality of life (Kansas City Cardiomyopathy Questionnaire), neurohumoral and inflammatory biomarkers (including urinary biomarkers), and glycaemic measures.

Signs and symptoms of heart failure included: paroxysmal nocturnal dyspnoea, fatigue, oedema, dyspnoea at rest, exertional dyspnoea, orthopnoea, rales, jugular venous distension, presence of a third heart sound, and NYHA classification. Extensive echocardiographic measures of cardiac size and ventricular function included: left ventricular (LV) end-diastolic and end-systolic volume/volume index (EDV/ESV and EDVi/ESVi), LVEF, LV internal diastolic dimension (LVIDD) and LV internal systolic dimension , LV posterior wall thickness, LV mass/mass index (LVM/LVMi), left atrial (LA) volume, mitral regurgitation (MR) area area, MR area to LA area ratio, right ventricular fractional area change, and Tei index. A number of Doppler indices were also measured including: peak mitral valve Doppler *E* wave velocity, peak *A* wave velocity, *E*/*A* ratio, deceleration time, peak early diastolic (E_m), and peak late diastolic (A_m) annular velocities. Neurohumoral and inflammatory biomarkers included; high-sensitivity C-reactive protein, interleukin 6, tumour necrosis factor alfa, matrix metalloprotease 9, amino-terminal propeptide of type III procollagen (PIIINP), plasma renin concentration, plasma renin activity, insulin-like growth factor, 24 h urinary aldosterone, sodium, protein, and creatinine. Glycaemic measures included: fasting plasma glucose, insulin, glycated haemoglobin (HbA1c), and homeostatic model assessment insulin resistance.

Although urinary protein excretion was a pre-specified endpoint in ALOFT, UACR was not a protocol-specified analysis and was measured after study completion in patients with available urine samples. Urinary albumin was measured using Roche Immunoturbidimetry (CRL Medinet Inc., Lenexa, KS, USA). Glomerular filtration rate was estimated (eGFR) using the four-variable modification of diet in renal disease formula.[12]

Statistical analyses

These analyses were restricted to the patients for whom a UACR was available. Macroalbuminuria was defined as an UACR >25 mg/mmol in men and women, microalbuminuria as an UACR 2.5–25 mg/mmol in men, and 3.5–25 mg/mmol in women.[13] Associations between the baseline characteristics, glycaemic indices, echocardiographic measurements, neurohumoral measurements, and UACR category (normo-, micro-, and macro-) were tested using linear regression and logistic regression where appropriate. Linear regression models were then used to analyse the unadjusted associations between all baseline variables and UACR (as a continuous variable). Urinary albumin creatinine ratio was positively skewed and analysed as log [concentration] in a continuous fashion. Any variable with a *P*-value ≤0.05 for the unadjusted associations was included in the adjusted analyses, together with age and sex. Two types of sensitivity analyses were performed. First, the analysis was run for the whole dataset and non-diabetics only, to test the sensitivity of the results to the inclusion of diabetic patients. Secondly, the analysis was run for the complete cases and multiple imputations using the switching regression technique to test the sensitivity of the results to the missing data. All statistical analyses were performed with Stata version 10.

Results

Baseline characteristics

Overall, 302 patients were randomized into the ALOFT study. A UACR was available in 190 (63%) patients. Of these, 107 (56%) had normal albuminuria, 63 (33%) had microalbuminuria, and 20 (11%) had macroalbuminuria. The baseline clinical characteristics of patients in each category are shown in *Table 1*. Patients without an UACR measurement did not differ notably from those with such a measurement (Supplementary material online, *Appendix*).

Table 1 Baseline characteristics

	Normoalbuminuria	Macroalbuminuria	Microalbuminuria	*P*-value[a]	
	(*n* = 107)	(*n* = 20)	(*n* = 63)	1	2
Mean (SD) age (year)	69 (10)	63 (14)	69 (9)	0.02	0.7
≥65 year (%)	73	45	75	0.02	0.8
Male sex (%)	73	80	83	0.5	0.2
Caucasian (%)	98	90	97	0.09	0.6
Physiologic measurements (mean, SD)					
LVEF (%)[b]	31.1 (5.4)	32.9 (5.2)	30.2 (5.0)	0.2	0.3
BMI (kg/m^2)	27.5 (5.2)	28.5 (5.9)	27.6 (4.6)	0.4	0.9
Obese (%)[c]	29	20	18	0.4	0.09
Systolic blood pressure (mmHg)	126.6 (18.4)	132.9 (18.1)	131.1 (18.0)	0.2	0.1
Diastolic blood pressure (mmHg)	77.0 (10.2)	82.9 (13.3)	78.2 (11.5)	0.04	0.5
Heart failure history					
Duration (year)	4.73 (5.31)	3.62 (3.33)	4.20 (4.08)	0.2	0.9
LVEF (%)[b] ≤40%	93	94	96	0.7	0.8
Aetiology[d] (%)					
Ischaemic	51	45	64	0.3	0.6
Hypertensive	14	35	14		
Idiopathic	26	15	18		
Other	9	5	4		
NYHA class (%)					
I	1 (1)	0	0	0.9	0.2
II	68 (64)	12 (60)	37 (59)		
III	38 (36)	8 (40)	24 (38)		
IV	0	0	2 (3)		
Medical history (%)					
Myocardial infarction	33.6	30.0	52.4	0.8	0.02
Angina pectoris	15.9	20.0	25.4	0.7	0.1
Diabetes mellitus	26.2	60.0	47.6	0.004	0.005
eGFR mL/min/1.73 m^2	68.3 (18.9)	66.6 (23.7)	60.7 (18.1)	0.7	0.01
Renal function category (%)					
eGFR<29 mL/min/1.73 m^2	0.9	0	1.6	0.6	0.006
eGFR≥29—<60 mL/min/1.73 m^2	28.0	40.0	55.6		
eGFR≥60—<90 mL/min/1.73 m^2	55.1	40.0	34.9		
eGFR≥90 mL/min/1.73 m^2	14.0	20.0	7.9		
Laboratory measurements (blood)					
Creatinine (μmol/L)	94.5 (35.7)	96.7 (45.4)	103.0 (48.3)	0.6	0.6
BUN (mmol/L)	9.0 (6.2)	9.6 (6.0)	10.4 (6.2)	0.7	0.04
Uric acid (μmol/L)	0.8 (1.8)	1.4 (3.4)	1.1 (2.2)	0.5	0.1
Potassium (mmol/L)	4.4 (0.6)	4.4 (0.5)	4.4 (0.6)	0.9	0.9
Cholesterol (mmol/L)	102.6 (3.4)	102.9 (3.2)	102.6 (3.2)	0.7	0.9
Albumin (g/L)	41.7 (8.9)	36.8 (13.1)	39.0 (11.8)	0.06	0.1
Haemoglobin (g/L)	134.2 (31.0)	127.1 (43.0)	126.9 (39.5)	0.4	0.2
Laboratory measurements (urine)					
Sodium mmol/day	153.9 (80.6)	174.6 (117.9)	164.0 (71.1)	0.7	0.2
Protein mg/day (*n* = 171)	113.5 (67.4)	1547.7 (2032.7)	193.5 (109.4)	<0.001	<0.001
Creatinine mmol/day (*n* = 189)	13.1 (10.7)	9.9 (5.3)	9.4 (4.5)	0.3	0.01
Aldosterone pmol/L (*n* = 180)	42.9 (51.5)	26.4 (21.4)	29.2 (21.8)	0.2	0.6
Treatment (%)					
ACE inhibitor	84	70	81	0.1	0.6

Continued

Table 1 *Continued*

	Normoalbuminuria ($n = 107$)	Macroalbuminuria ($n = 20$)	Microalbuminuria ($n = 63$)	*P*-value[a] 1	2
ARB	15	25	19	0.3	0.5
Beta-blocker	96	95	86	0.8	0.02
Aldosterone antagonist	31	20	32	0.3	0.9

LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; BMI, body mass index; NYHA, New York Heart Association; BUN, blood urea nitrogen (urea); ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a]Comparison 1: macroalbuminuria vs. normal; comparison 2: microalbuminuria vs. normal.
[b]Measured in core laboratory.
[c]BMI $\geq$ 30 kg/m^2.
[d]Investigator reported.

Table 2 Glycaemic indices

	Normoalbuminuria ($n = 107$)	Macroalbuminuria ($n = 20$)	Microalbuminuria ($n = 63$)	*P*-value[a] 1	2
Fasting plasma glucose (mmol/L)					
Diabetic ($n = 69$)	8.2 (2.6)	8.6 (2.0)	8.1 (2.0)	0.6	0.9
Non-diabetic ($n = 119$)	5.5 (0.7)	5.7 (0.6)	5.5 (0.7)	0.3	0.9
All ($n = 188$)	6.2 (1.9)	7.4 (2.1)	6.7 (2.0)	0.009	0.08
HbAlc %					
Diabetic ($n = 68$)	6.9 (1.4)	9.0 (2.5)	7.7 (2.0)	0.002	0.1
Non-diabetic ($n = 118$)	5.9 (0.4)	6.3 (1.1)	6.0 (0.5)	0.07	0.4
All ($n = 186$)	6.2 (0.9)	7.9 (2.4)	6.8 (1.7)	$<$0.001	0.004
Insulin pmol/L					
Diabetic ($n = 58$)	133.2 (86.4)	140.7 (131.4)	140.0 (81.5)	0.9	0.8
Non-diabetic ($n = 94$)	84.2 (62.0)	73.1 (48.4)	85.6 (83.1)	0.9	0.7
All ($n = 152$)	97.7 (72.4)	112.9 (108.5)	111.3 (86.1)	0.6	0.2

[a]Comparison 1: macroalbuminuria vs. normal; comparison 2: microalbuminuria vs. normal.

Patients with macroalbuminuria

Patients with macroalbuminuria were younger than those with normoalbuminuria, had a higher diastolic blood pressure, and were much more likely to be diabetic (and to have higher fasting plasma glucose and HbA1c, *Table 2*). There were no significant differences in the use of heart failure disease-modifying therapies. Patients with macroalbuminuria had increased LV wall thickness compared with patients with normal albumin excretion (*Table 3*). They also had smaller left ventricles and less MR (*Table 3*). There were no statistically significant differences in neurohumoral or inflammatory markers (*Table 4*) compared with patients with normal albumin excretion, although there was a trend towards higher NT-proBNP levels in patients with macroalbuminuria.

Patients with microalbuminuria

Patients with microalbuminuria differed from those with macroalbuminuria (*Table 1*). They were older than patients with macroalbuminuria and similar in age to those with normal albumin excretion. The prevalence of diabetes in patients with microalbuminuria was significantly higher than in those with normoalbuminuria (but was less than in patients with macroalbuminuria). Mean eGFR was lower in patients with microalbuminuria, compared with the other two groups. Over half of patients with microalbuminuria had a substantially reduced eGFR ($<$60 mL/min/1.73 m^2); blood urea nitrogen was also higher in these patients. Glycated haemoglobin was higher in all patients (diabetic and non-diabetic) with microalbuminuria compared with those with normoalbuminuria (*Table 2*). Of patients with a fasting blood glucose measurement, 2 of 33 (6.0%) of these with microalbuminuria had a level $\geq$7.0 mmol/L, compared with 5 of 79 (6.3%) of those with normoalbuminuria. Prior myocardial infarction was more prevalent in patients with microalbuminuria. Patients with microalbuminuria were less likely to be treated with a beta-blocker than those with a normal UACR. Ventricular wall thickness was increased in patients with microalbuminuria compared

Table 3 Echocardiographic measurements

	Normoalbuminuria ($n = 107$)	Macroalbuminuria ($n = 20$)	Microalbuminuria ($n = 63$)	*P*-value[a] 1	2
LV-SWT (cm) ($n = 169$)	0.92 (0.11)	0.98 (0.11)	0.94 (0.12)	0.04	0.3
LV-PWT (cm) ($n = 169$)	0.89 (0.11)	0.93 (0.11)	0.92 (0.11)	0.2	0.05
LVM (g) ($n = 169$)	236.9 (51.7)	227.8 (37.2)	244.6 (45.6)	0.5	0.3
LVMi (g/m^2) ($n = 167$)	125.3 (26.2)	119.0 (15.9)	129.1 (31.3)	0.4	0.4
LVIDD (cm) ($n = 169$)	6.3 (0.6)	5.9 (0.6)	6.3 (0.5)	0.02	0.9
LVISD (cm) ($n = 169$)	5.2 (0.6)	4.8 (0.6)	5.2 (0.5)	0.02	0.9
EDVi (mL/m^2) ($n = 170$)	123.4 (26.4)	109.5 (19.7)	121.1 (27.1)	0.05	0.6
ESVi (mL/m^2) ($n = 170$)	85.8 (22.9)	74.3 (18.0)	85.1 (22.2)	0.05	0.8
LAV (mL) ($n = 170$)	105.3 (29.4)	98.0 (24.9)	103.9 (20.2)	0.3	0.7
MR area (cm^2) ($n = 123$)	8.9 (4.7)	5.1 (1.6)	7.9 (2.9)	0.006	0.2
MR area/LA area ratio ($n = 156$)	31.7 (14.5)	19.9 (8.9)	29.6 (11.0)	0.008	0.4
Peak E (cm/s) ($n = 138$)	81.0 (26.9)	77.4 (21.6)	78.1 (26.1)	0.6	0.5
Peak A (cm/s) ($n = 134$)	61.3 (30.1)	55.3 (31.8)	60.8 (29.6)	0.5	0.9
E/A ratio ($n = 134$)	1.8 (1.4)	2.0 (1.0)	1.9 (1.5)	0.5	0.9
DT (second) ($n = 156$)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.8	0.6
E_m (cm/s) ($n = 140$)	6.9 (3.0)	7.0 (3.6)	6.6 (2.6)	0.9	0.6
E/E′ ($n = 122$)	9.2 (28.2)	6.5 (2.9)	6.1 (3.4)	0.8	0.8
RV-FAC (%) ($n = 113$)	39.5 (5.9)	42.6 (5.8)	39.5 (5.7)	0.09	0.9
TEi's index ($n = 151$)	0.6 (0.3)	0.6 (0.2)	0.6 (0.3)	0.7	0.4

All results are shown as mean (SD).
EDVi, end-diastolic volume index; ESVi, end-systolic volume index; MR, mitral regurgitation; LVIDD, left ventricular internal diastolic dimension; LVISD, left ventricular internal systolic dimension; LAV, left atrial volume; LVEF, left ventricular ejection fraction; LA, left atrium; DT, deceleration time; Peak E, peak early transmitral flow velocity; Peak A, peak atrial transmitral flow velocity; E_m, early diastolic peak velocity of the mitral annulus; *E/E′*, ratio of mitral velocity to early diastolic velocity of the mitral annulus; RV-FAC, right ventricular fractional area change; LV-SWT, left ventricular septal wall thickness; LVM, left ventricular mass; TEI, index of Tei (isovolumetric contraction time+isovolumetric relaxation time/ejection time); LV-PWT, left ventricular posterior wall thickness.
[a]Comparison 1: macroalbuminuria vs. normal; comparison 2: microalbuminuria vs. Normal.

Table 4 Neurohumoral measurements (plasma unless stated otherwise)

	Normoalbuminuria ($n = 107$)	Macroalbuminuria ($n = 20$)	Microalbuminuria ($n = 63$)	*P*-value[a] 1	2
NT-proBNP (pg/mL) ($n = 183$)	2287.5 (4281.8)	2612.0 (2060.2)	2496.6 (2339.3)	0.06	0.07
BNP (pg/mL) ($n = 190$)	283.6 (264.0)	288.7 (343.7)	372.6 (326.8)	0.4	0.3
Aldosterone (pmol/L) ($n = 178$)	300.5 (376.1)	209.4 (193.5)	319.3 (266.2)	0.1	0.2
PRC (ng/L) ($n = 178$)	69.2 (107.5)	69.4 (113.9)	61.5 (110.2)	0.9	0.2
PRA (ng/mL/h) ($n = 180$)	8.1 (12.3)	7.4 (14.0)	6.3 (11.4)	0.6	0.1
hs CRP (mg/L) ($n = 156$)	5.2 (7.3)	5.6 (8.8)	4.6 (5.6)	0.6	0.8
hs IL6 (ng/L) ($n = 134$)	4.5 (3.8)	5.6 (4.9)	4.5 (3.9)	0.5	0.9
TNF-α (ng/L) ($n = 136$)	2.2 (2.3)	1.7 (1.0)	2.9 (4.1)	0.2	0.09
PIIINP (μg/L) ($n = 139$)	4.3 (1.4)	4.7 (2.3)	5.4 (2.3)	0.4	0.001
IGF (μg/L) ($n = 34$)	98.5 (26.2)	133.0 (1.4)	92.5 (30.9)	0.1	0.6

NT-proBNP, N-terminal pro B-type natriuretic peptide; PRC, plasma renin concentration; PRA, plasma rennin activity.
[a]Comparison 1: macroalbuminuria vs. normal; comparison 2: microalbuminuria vs. normal

with those with normal albumin excretion but cavity size was similar, as was the degree of MR (in contrast to patients with macroalbuminuria, *Table 3*).

Patients with microalbuminuria had numerically higher plasma BNP concentrations and significantly elevated PIIINP concentrations compared with those with a normal UACR (there was

Table 5 Significant unadjusted and adjusted associations with log-urinary albumin creatinine ratio —all patients

Variable	Unadjusted				Adjusted			
	Coefficient*	SE	95% CI	*P*-value	Coefficient*	SE	95% CI	*P*-value
Age, year	−0.019	0.012	−0.041: 0.003	0.09	−0.022	0.010	−0.041: −0.003	0.024
Sex, female	−0.013	0.278	−0.562: 0.535	0.962	−0.336	0.222	−0.774: 0.102	0.132
SBP, mmHg	0.014	0.006	0.002: 0.027	0.024	0.008	0.006	−0.003: 0.020	0.165
DBP, mmHg	0.020	0.010	0.000: 0.041	0.054	0.009	0.010	−0.011: 0.030	0.370
DM	0.742	0.237	0.274: 1.210	0.002	0.069	0.265	−0.458: 0.596	0.796
eGFR, mL/min//1.73 m^2	−0.012	0.006	−0.024: 0.000	0.052	−0.013	0.005	−0.023: −0.002	0.015
Albumin, (blood) g/L	−0.031	0.011	−0.052: −0.009	0.006	−0.006	0.009	−0.023: 0.011	0.478
FBG, mmol/L	0.186	0.059	0.070: 0.302	0.002	−0.045	0.064	−0.171: 0.081	0.478
HbA1c, %	0.466	0.071	0.326: 0.607	<0.001	0.391	0.084	0.226: 0.557	<0.001
LV-SWT, cm	2.773	1.087	0.627: 4.919	0.012	0.694	0.906	−1.114: 2.501	0.446
LVIDD, cm	−0.496	0.164	−0.821: −0.171	0.003	−0.525	0.168	−0.858: −0.191	0.002
MR, cm^2	−0.074	0.035	−0.143: −0.006	0.034	−0.056	0.033	−0.123: 0.011	0.098
SDANN, ms	−0.012	0.101	−0.022: −0.003	0.014	−0.000	0.003	−0.007: 0.006	0.956
Urine Aldo, pmol/L	−0.006	0.002	−0.010: −0.002	0.009	−0.009	0.002	−0.005: 0.004	0.697
NT-proBNP, pg/mL	0.328	0.005	0.128: 0.527	0.001	0.287	0.088	0.112: 0.462	0.002

*Per 1 unit change for continuous variables

SE, standard error; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated haemoglobin;

LV-SWT, left ventricular septal wall thickness; LVIDD, left ventricular internal diastolic dimension; MR, mitral regurgitation; SDANN, standard deviation of averages of NN; aldo, aldosterone; NT-proBNP, N-terminal pro B-type natriuretic peptide.

no significant difference between those with macro- and normoalbuminuria, *Table 4*).

Associations of urinary albumin creatinine ratio: all patients (with and without diabetes)

In univariate analyses, many of the baseline variables shown in *Tables 1–4* were significantly associated with log[UACR] (*Table 5*). However, after adjustment, only age, eGFR, HbA1c, LVIDD, and NT-proBNP were significantly associated with log[UACR] (*Table 5*). Each year increase in age was associated with a 0.022 mg/mmol decrease in log[UACR] and each centimetre increase in LVIDD was associated with a 0.525 mg/mmol decrease in log[UACR]. Every millilitre per minute per 1.73 m^2 decrease in eGFR was associated with a 0.013 mg/mmol increase in log[UACR]. Each percentage increase in HbA1c was associated with a 0.391 mg/mmol increase in log[UACR]. Finally, every picogram per millilitre increase in log[NT-proBNP] was associated with an increase of 0.287 mg/mmol in log[UACR].

Associations of urinary albumin creatinine ratio: patients without diabetes only

Removal of the patients with diabetes from the dataset reduced the number of variables with a significant unadjusted association with log[UACR] (*Table 6*). In the adjusted analysis, LVIDD, HbA1c, and log[NT-proBNP] remained significantly associated with log[UACR] (*Table 6*). For every 1% increase in HbA1c and 1 pg/mL increase in log[NT-proBNP], there was an associated 0.655 and 0.291 mg/mmol, respectively, increase in log[UACR]. Each centimetre increase in LVIDD was associated with a 0.534 mg/mmol decrease in log[UACR].

Effect of aliskiren on N-terminal pro B-type natriuretic peptide and urinary albumin creatinine ratio

As reported previously, the ratio of end-of-study to baseline geometric mean NT-proBNP was 0.96 (0.75, 1.24) in the placebo group and 0.73 (0.57, 0.93) in the aliskiren group with an aliskiren/placebo ratio of 0.75 (0.61, 0.94), $P = 0.011$.[8] The equivalent ratios for UACR were 0.89 (0.61, 1.30), 0.96 (0.67, 1.37), and 1.08 (0.78, 1.48), $P = 0.653$.

Discussion

We found that 33% (63 of 190) of patients with stable chronic heart failure had microalbuminuria and 11% (20 of 190) had macroalbuminuria. These findings are noticeably similar to those from a larger sub-study of patients with chronic heart failure, the Candesartan in Heart failure: Assessment or Reduction in Cardiovascular Mortality and Morbidity (CHARM) study, where 30 and 11% had microalbuminuria and macroalbuminuria, respectively.[1] Our characterization of patients with microalbuminuria and macroalbuminuria also confirms and expands the description of these patients in both CHARM and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Heart Failure study.

Table 6 Significant unadjusted & adjusted associations with log-urinary albumin creatinine ratio – non-diabetic patients

Variable	Unadjusted				Adjusted			
	Coefficient[a]	SE	95% CI	*P*-value	Coefficient*	SE	95% CI	*P*-value
Age, years	−0.010	0.012	−0.035: 0.014	0.401	−0.016	0.134	−0.043: 0.012	0.266
Sex, female	−0.102	0.300	−0.697: 0.493	0.735	−0.441	0.302	−1.043: 0.161	0.149
SBP, mmHg	0.015	0.008	0.000: 0.030	0.055	0.012	0.008	-0.003: 0.027	0.117
DBP, mmHg	0.022	0.013	−0.004: 0.047	0.100	−0.004	0.014	−0.032: 0.023	0.753
eGFR, mL/min/1.73 m^2	−0.005	0.007	−0.019: 0.008	0.423	−0.010	0.007	−0.024: 0.003	0.142
Albumin, (blood) g/L	−0.009	0.014	−0.037: 0.019	0.532	0.001	0.012	−0.023: 0.025	0.958
FBG, mmol/L	0.053	0.205	−0.352: 0.459	0.795	0.004	0.181	−0.357: 0.364	0.984
HbA1c, %	0.485	0.259	−0.029: 0.999	0.064	0.655	0.259	0.137: 1.173	0.014
LV-SWT, cm	2.941	1.303	0.357: 5.524	0.026	1.169	1.149	−1.128: 3.466	0.313
LVIDD, cm	−0.446	0.217	−0.876: −0.016	0.042	−0.534	0.214	−0.963: −0.105	0.016
MR, cm^2	−0.040	0.037	−0.114: 0.034	0.286	−0.053	0.032	−0.117: 0.011	0.105
SDANN, ms	−0.003	0.006	−0.014: 0.009	0.625	0.004	0.003	−0.003: 0.010	0.282
Urinary Aldo, pmol/L	−0.007	0.003	−0.012: −0.001	0.025	−0.001	0.003	−0.007: 0.005	0.713
NT-proBNP, pg/mL	0.258	0.106	0.081: 0.500	0.007	0.291	0.096	0.101: 0.480	0.003

[a]Per 1 unit change for continuous variables.
SE, standard error; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycated haemoglobin;
LV-SWT, left ventricular septal wall thickness; LVIDD, left ventricular internal diastolic dimension; MR, mitral regurgitation; SDANN, standard deviation of averages of NN; aldo, aldosterone; NT-proBNP, N-terminal pro B-type natriuretic peptide.

There were differences between patients with microalbuminuria and macroalbuminuria and both groups with elevated urinary albumin excretion clearly differed from those with a normal UACR.

Compared with patients with a normal UACR, patients with microalbuminuria had a greater prevalence of diabetes and a lower eGFR. There were even greater differences between those with macroalbuminuria and normal albumin excretion, with the exception of eGFR that was similar (emphasizing the discordance between increased urinary albumin excretion and decreased glomerular filtration rate).[14,15] In addition, patients with macroalbuminuria were younger had higher diastolic blood pressure and HbA1c, smaller ventricles, and less MR. In other words, the patients with macroalbuminuria appeared to have evidence of less well-controlled diabetes, with more complications. Interestingly, they also seemed to have heart failure of similar symptomatic severity to patients with normal albumin excretion, despite less severe cardiac structural and functional abnormalities.

It is important to note, however, that increased albumin excretion in these patients with heart failure was not simply a marker of diabetes. Although 43% of diabetic patients had microalbuminuria (and 17% macroalbuminuria), 28% of non-diabetic patients also had microalbuminuria (and 7% macroalbuminuria), strikingly similar results to 2310 patients with UACR measured in the CHARM programme where 27% of non-diabetic patients had microalbuminuria and 6% had macroalbuminuria.[1] This raises the interesting pathophysiological question of why the prevalence of microalbuminuria in non-diabetic patients with heart failure is two to three times that in subjects of similar age in the general population. For example, in the Prevention of Renal and Vascular End Stage Disease study, the prevalence of microalbuminuria in subjects aged 60–74 years was 10.4% [95% confidence interval (CI) 9.8–11.0].[16] We explored some of the suggested mechanisms underlying increased albumin excretion in cardiovascular disease, particularly systemic atherosclerosis and inflammation.[2,4,17–21] We did find that patients with microalbuminuria had a higher prevalence of coronary heart disease than those with a normal excretion. On the other hand, we found no evidence of heightened inflammation in patients with microalbuminuria, at least as determined by plasma biomarkers. Activation of the renin angiotensin aldosterone system (RAAS) has been suggested to play a causal role in increasing urinary albumin excretion, possibly by causing intraglomerular hypertension.[4,17–20] It is therefore noteworthy that we found a high prevalence of increased albumin excretion despite treatment with at least one blocker of the RAAS, given that these agents reduce albumin excretion.[22] Furthermore, we did not find evidence of greater activation of the RAAS in patients with microalbuminuria or macroalbuminuria. We did, however, observe that HbA1c in non-diabetic patients with microalbuminuria was somewhat higher than in non-diabetic patients with normal albumin excretion and in non-diabetic patients HbA1c was an independent predictor of UACR. This suggests that even non-diabetic levels of glucose are in some way associated with glomerular damage in patients with heart failure although only a small percentage (~7%) of non-diabetic patients had undiagnosed diabetes, as indicted by a single elevated fasting plasma glucose measurement.

Another potential mechanism for increased albumin excretion in heart failure was suggested by the association between

NT-proBNP and UACR, independent of diabetic status, which we believe to be a novel and interesting finding. Natriuretic peptides may increase glomerular and tubular protein excretion,[23] and consequently be mechanistically linked to increased albumin excretion, or they may be part of the same pathophysiological process causal to elevated urinary albumin. Hypervolaemia and increased central venous pressure may lead to renal venous congestion, known to cause proteinuria in animals and a similar mechanism may operate in patients with heart failure.[10,24] If true, this may explain our findings regarding the association between NT-proBNP and albuminuria. However, there were no significant differences in LVEF, duration of heart failure, aetiology of heart failure, or symptom severity in patients with elevated urinary albumin compared with patients with normal urinary albumin and there was a puzzling inverse association between LVIDD and UACR.

Aliskiren did not reduce UACR, a finding consistent with CHARM in which candesartan also had no effect on UACR over a much longer period of treatment (despite reducing blood pressure). These observations suggest that the proteinuric response to RAAS blockade in heart failure is different than in diabetic nephropathy.[25]

Our study has limitations one of which, the relatively small sample size, may explain why some variables showed only a trend towards statistical significance. On the other hand, the large number of comparisons made in this exploratory study may have led to chance findings of spurious statistical significance.

In summary, increased, urinary albumin excretion is common in heart failure, particularly among diabetics, although it was still detected in 35% of non-diabetic patients. Elevated UACR was not associated with markers of inflammation or RAAS activation. It was, however, associated with increased plasma HbA1c and NT-proBNP levels.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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