Long-term changes in urinary albumin excretion are closely associated with cardiovascular outcomes in patients with resistant hypertension

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Background

- Patients with resistant hypertension (RH) have higher prevalence of target organ damage and cardiovascular disease (CVD) than subjects with controlled blood pressure (BP)
- In patients with confirmed RH, the main determinants that have been associated with cardiovascular risk are ambulatory BPs and subclinical organ alterations, such as left ventricular hypertrophy.
- Attending to renal parameters, changes in urinary albumin excretion (UAE) and both serum creatinine and estimated glomerular filtration rate are well-known predictors of CVD in general population ***(Gerstein, J Am Soc Nephrol – 2001; Sarnak, Circulation – 2003; Hallan, Arch Intern Med – 2007).***
- However, their possible prognostic value in RH patients is rather unknown.

Objective

The aim of this study was to determine the ability of renal function and albuminuria to predict CVD in RH patients.

Methods

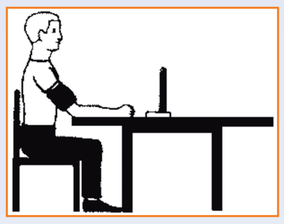
- Long-term observational multicenter study of **143** patients with RH attended in specialized hypertension clinics at 4 university hospitals in Catalonia, Spain.
- Patients were consecutively recruited between April 2004 and January 2006.
- All patients were submitted to a standard protocol based on records of clinical characteristics and conditions, basic laboratory evaluation, 2D-echocardiography with left ventricular mass index calculation and 24h-ambulatory blood pressure monitoring (24h-ABPM).
- A second medical and laboratory evaluation at follow-up was available for **133** subjects in this cohort, and those were the patients included in this study.

❍ **Resistant hypertension (RH)** was defined as BP which remains above ≥140 and/or 90mmHg despite a prescribed therapeutic schedule with an appropriate combination of ≥3 full-dose antihypertensive drugs (a diuretic included).
❍ **Renal function** was assessed by both serum creatinine determination and estimated glomerular filtration rate (eGFR) according to the CKD-EPI (Chronic Kidney Disease-Epidemiology Collaborative) equation.
❍ **Microalbuminuria** (MA) was defined as a urinary albumin/creatinine ratio (UACR) ≥30 mg/g, averaged from three first-morning-void urine samples.

BP measurement:

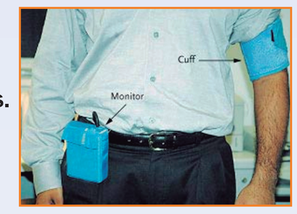
Office BP measurement

- Subjects rested for 5 minutes in the sitting position, BP being measured afterwards thrice using a validated oscillometric semiautomatic device *(Omron 705IT, Kyoto, Japan)*, with appropriated sized-cuffs, each measurement spaced 2 min from each other.
- The average of these BP records obtained in two separated visits was assumed as the definitive office BP value considered in this study.
- Office BP measurement was also evaluated in this way in a single follow-up visit.



24h-Ambulatory BP monitoring (ABPM)

- All patients underwent a 24h-ABPM with a validated Spacelabs-90207 device *(Issaquah, WA, USA)* when entering the study.
- Ambulatory BP recordings were carried out on a working day, starting at around 8-10, at 20-min intervals throughout both the ***awake*** (from 10 to 20 h) and the ***asleep*** (from 0 to 6 h) periods.
- A 24h-ABPM of good technical quality (percentage of valid readings higher than 80%) was a mandatory requisite to enter the study; otherwise, a second 24-ABPM was carried out.
- ***True-RH*** was confirmed if 24h-systolic BP was ≥130 mmHg and/or 24h-diastolic BP was ≥80 mmHg.



- **EXCLUSION CRITERIA:**
  - ❍ secondary hypertension
  - ❍ stage 4 or 5 of chronic kidney disease of any etiology
  - ❍ subjects on long-term corticosteroid or nonsteroidal anti-inflammatory therapies
  - ❍ poor adherent (according to a standard validated questionnaire) patients
  - ❍ patients with any acute disease or who had suffered a CV event in the earlier six months

Statistical analysis:

- Bivariate comparisons between patients with and without CV outcomes were performed through **unpaired *t* tests** or **ANOVA** in continuous data, by **Mann-Whitney-U test** in asymmetrically distributed data, and by χ^2 **test** in categorical data.
- A **repeated measures analysis of variance** was performed to assess the possible association of renal parameters at baseline and follow-up with the composite CV end-point. Analyses were performed after adjustment for systolic BP both at baseline and during follow-up and for previous CV disease. To evaluate the association of UACR and MA with the primary composite outcome, analyses were also adjusted for creatinine clearance both at baseline and follow-up, in addition to the aforementioned confounders. Because of skewed distribution, UACR was tested after log-transformation.
- To evaluate the prognostic value of changes in UACR on the occurrence of the composite CV outcome, patients were divided into 4 subgroups, according to the evolution of UACR from baseline to follow-up: *persistent normoalbuminuria, development of MA, regression of MA and persistent MA*. **Cox regression analyses** were therefore performed.
- A **logistic regression model** was developed to state the overall risk of CV outcomes for patients with MA at follow-up, i.e., patients belonging to the *development of MA* and persistent *MA* groups. Hazard ratio and corresponding 95% confident intervals are given.

Primary endpoint: combined variable consisting of the first occurrence of a nonfatal cardiovascular event (myocardial infarction, stroke, heart failure hospitalization, coronary or peripheral revascularization) or cardiovascular death.

Results

- A total of 133 patients entered the study, since 10 subjects (7%) of those initially enrolled were lost to follow-up.
- A complete laboratory analysis and office BP measurements were obtained around 6 years after entering the study
- Median follow-up (p25; p75): 73 months (52.5; 82.5)
- Twenty-six CV events occurred in the 22 patients (16.5%) who reached the primary composite outcome. There were also 9 non-CV deaths.

Table 1. Baseline characteristics of RH subjects without or with CV disease at follow-up.

	Patients with CVD n = 22	Patients without CVD n = 111	p-value
Clinical data			
Age (years)	65.7 ± 7.7	59.8 ± 9.4	0.006
Sex male, n (%)	13 (59)	65 (59)	0.963
BMI (Kg/m²)	30.9 ± 5.4	31.1 ± 4.9	0.893
Diabetes, n (%)	8 (36)	32 (29)	0.611
Dyslipidemia, n (%)	11 (50)	60 (54)	0.817
Smokers, n (%)	4 (18)	18 (16)	0.761
Duration of hypertension (years)*	15 (10; 25)	15 (6.5; 20)	0.602
Previous history of CVD, n (%)	10 (45)	20 (18)	0.010
Non RAS blockade, n (%)	1 (5)	4 (4)	0.832
True-RH, n (%)†	15 (68)	82 (74)	0.599
Renal laboratory parameters			
SCr (µmol/L)	105.2 ± 27.4	93.7 ± 23.0	0.036
eGFR (mL/min/1.73m²)	59.8 ± 16.6	70.4 ± 17.2	0.011
eGFR< 60mL/min/1.73m², n (%)	12 (55)	27 (24)	0.006
UACR (mg/g)*	23.8 [6.8; 73.6]	17.3 [7; 76.3]	0.797
Microalbuminuria, n (%)	10 (45)	45 (41)	0.813
Echocardiographic data			
LVMI (g/m²)	144.0 ± 42.6	136.6 ± 46.3	0.490
LVH, n (%)	15 (68)	70 (63)	0.808

CVD = cardiovascular disease; **BMI** = body mass index; **RAS** = renin-angiotensin system; **RH** = resistant hypertension; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **SCr** = serum creatinine; **eGFR** = estimated glomerular filtration rate; **UACR** = urinary albumin/creatinine ratio; **LVH** = left ventricular hypertrophy; **LVMI** = left ventricular mass index.
* Data are given as median (p25; p75). Remaining data are given as mean±SD or percentages.
† True-RH defined as 24h-BP ≥130/80 mmHg.

Table 2. Blood pressure measurements in resistant hypertensive subjects with or without cardiovascular disease at follow-up.

	Patients with CVD n = 22	Patients without CVD n = 111	p-value
Blood pressure at baseline			
Office-SBP (mmHg)	156.9 ± 15.3	157.2 ± 17.3	0.918
Office-DBP (mmHg)	85.6 ± 14.6	89.8 ± 12.0	0.154
Day-SBP (mmHg)	139.3 ± 15.2	142.3 ± 15.0	0.405
Day-DBP (mmHg)	77.6 ± 15.2	83.0 ± 11.5	0.131
Night-SBP (mmHg)	134.7 ± 18.8	134.1 ± 18.7	0.891
Night-DBP (mmHg)	71.5 ± 13.8	74.1 ± 11.4	0.353
24h-SBP (mmHg)	139.7 ± 16.0	140.6 ± 15.3	0.821
24h-DBP (mmHg)	76.6 ± 14.2	80.2 ± 10.9	0.269
Blood pressure at follow-up			
Office-SBP (mmHg)	139.6 ± 17.2	138.3 ± 20.5	0.762
Office-DBP (mmHg)	69.3 ± 10.8	76.1 ± 14.4	0.045

SBP = systolic blood pressure; **DBP** = diastolic blood pressure
Data are given as mean±SD

Microalbuminuria prevalence at follow-up was 67% and 28% in patients with and without CVD, respectively (p=0.002).

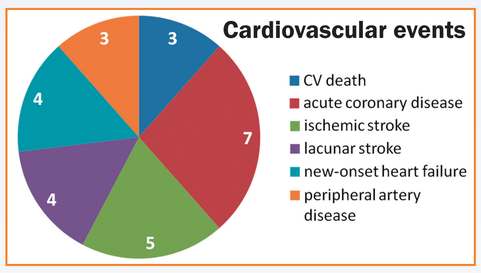


Table 3. Cardiovascular outcomes according to renal parameters at baseline and at follow-up.

Variable	With CVD		Without CVD		Unadjusted	Adjusted
	Baseline	Follow-up	Baseline	Follow-up	P	P
SCr (µmol/L)	105.2±27.4	108.9±36.0	93.7±23.0	90.2±37.1	0.006	0.068†
eGFR (mL/min/1.73m²)	59.8±16.6	60.8±25.2	70.4±17.2	73.6±19.0	0.003	0.117†
UACR (mg/g)*	23.8 (6.8-73.6)	66.2 (20.9-435)	17.3 (7-76.3)	16.8 (6-38)	0.012	0.045‡

CVD = cardiovascular disease; **SCr** = serum creatinine; **eGFR** = estimated glomerular filtration rate; **UACR** = urinary albumin/creatinine ratio.
* Data are given as median [p25; p75). Remaining data are given as mean±SD or percentages.
†adjusted for age, office systolic blood pressure both at baseline and during follow-up and previous CVD.
‡ adjusted for the aforementioned confounders plus eGFR both at baseline and at follow-up; UACR tested after log-transformation.

Table 4: Effect of changes in albuminuria at follow-up on the occurrence of CVD.

Variable	Patients with CVD n = 22	Patients without CVD n = 111
N_b – $N_{f\text{-}u}$	22%	53%
N_b – $MA_{f\text{-}u}$	28%	6%
MA_b – $N_{f\text{-}u}$	11%	19%
MA_b – $MA_{f\text{-}u}$	39%	21%

CVD = cardiovascular disease; **N** = normoalbuminuria; **MA** = microalbuminuria; **b** = baseline; **f-u** =follow-up.
Overall p=0.005.

Conclusions

- The long-term persistence or new development of microalbuminuria is independently associated with incident CVD in patients with RH.
- The determination of albuminuria is an excellent marker of long-term CV risk in patients with RH, beyond its value in the initial evaluation of the patient, and independently of estimated glomerular filtration rate.
- Albuminuria consolidates as a mandatory subclinical target organ damage marker to determine when following-up RH patients to better assess their overall cardiovascular risk.

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