ORGAN DAMAGE CHANGES IN RESISTANT HYPERTENSIVES RANDOMIZED TO RENAL DENERVATION OR SPIRONOLACTONE. THE DENERVHTA STUDY.

Short Title: SPIRONOLACTONE vs. DENERVATION IN ALBUMINURIA

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Abstract

Renal denervation (RDN) and spironolactone have both been proposed for the treatment of resistant hypertension (RH), but their effects on preclinical target organ damage have not been compared. Twenty-four patients with 24h-SBP ≥140 mmHg despite receiving ≥3 full-dose antihypertensive drugs, one a diuretic, were randomized to receive spironolactone or RDN. Changes (Δ) in 24h-BP, urine albumin excretion (UAE), arterial stiffness, carotid intima-media thickness and left ventricular mass index, were evaluated at 6 months. Mean baseline-adjusted difference (95%CI) between the two groups (Spironolactone vs.RDN) at 6 months in 24h-SBP was of-17.9 mmHg (-30.9 to -4.9); p=0.01. Mean baseline-adjusted (95%CI) ΔUAE was -87.2 (-164.5;-9.9) and -23.8 (-104.5;56.9), respectively; *p*=0.028. Mean baseline-adjusted (95%CI) variation of 24h-pulse pressure was -13.5 (-18.8;-8.2) and -2.1 (-7.9;3.7); respectively; *p*=0.006. The correlation of Δ24h-SBP with Δlog-UAE was r=0.713; *p*<0.001. At 6 months there is a reduction in albuminuria in RH patients treated with spironolactone as compared to RDN.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02039492

Keywords: end organ damage; renal denervation; spironolactone; albuminuria; arterial stiffness; left ventricular hypertrophy; carotid wall thickness.

Introduction

Patients whose blood pressure (BP) remains above goal in spite of the use of at least three antihypertensive drugs of different classes given at optimal doses, ideally one of them a diuretic, are considered to have resistant hypertension (RH) (1). Around 11-13% of hypertensive people are believed to have RH (2-5), prevalence that lowers to near 5% when secondary causes, non-adherence to drug treatment and white-coat resistant hypertension are reasonably discarded (6). Resistant hypertension is known to carry a higher cardiovascular risk than controlled BP, with an associated increased prevalence of major cardiovascular and renal outcomes and mortality (7). In the continuum of vascular disease, asymptomatic organ damage is considered as an intermediate stage and a determinant of overall cardiovascular risk. Four markers of organ damage (microalbuminuria, increased pulse wave velocity [PWV], left ventricular hypertrophy [LVH], and carotid plaques and/or increased wall thickness) have been shown to be reliable predictors of cardiovascular mortality independently of SCORE stratification (8). Remarkably, preclinical target organ involvement is more prevalent in patients with uncontrolled hypertension than in those with BP under control (9), therefore justifying their increased vascular risk. The last two decades have witnessed the development of new approaches to treat RH, with special focus on the non-pharmacological ones. Sympathetic renal denervation (RDN) showed initial promising results, although the randomized controlled trial Symplicity HTN-3 failed to demonstrate a significant BP decrease as compared to the sham control group (10). On the other hand, a major role for spironolactone, an old drug that acts as a mineralocorticoid receptor antagonist, has emerged to treat RH. Thus, in the ASPIRANT (Addition of Spironolactone in Patients with Resistant Arterial Hypertension) trial (11) spironolactone as an add-on treatment

showed significant decreases in BP. Recently, results from the PATHWAY-2 (Optimum Treatment for Drug-Resistant Hypertension) trial (12) have shown that spironolactone is superior to other drugs as add-on therapy in patients with RH. We designed a randomized clinical trial with a head-to-head comparison of these two strategies in patients with RH, reporting that spironolactone was superior to RDN in reducing 24h-ambulatory BP (13). As a pre-specified secondary outcome, we have also compared changes on markers of preclinical target organ damage between both add-on treatments, which are now reported.

Methods

Study Design and Patients

The DENERVHTA (DENERVación en HiperTensión Arterial) study is a prospective, multicentre, open-label, randomized, controlled trial (clinicaltrials.gov identifier: NCT02039492), aimed to compare changes on 24h-systolic BP (SBP) between patients with RH randomized to receive either RDN or spironolactone as add-on therapies. Details about the DENERVHTA trial have already been published elsewhere (13). In brief, all participants were aged between 18 and 80 years at study entry and had office SBP $\geq$ 150 mmHg and 24h-SBP $\geq$ 140 mmHg while on treatment with 3 or more full-dose antihypertensive medications, one of them a diuretic, but without mineralocorticoid receptor antagonists. Patients were randomized (in a 1:1 ratio) to receive RDN (one single operator, median 10 shots) or spironolactone (50 mg od), in addition to current antihypertensive treatment. Estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 or the occurrence of a major vascular event (myocardial infarction, unstable angina or stroke) within 6 months prior to study enrolment were exclusion criteria for entry into DENERVHTA trial. The primary endpoint was the between-group comparison of mean changes in ambulatory 24-h SBP from baseline to 6 months. Here we report additional analysis focused on the effect of both treatments on preclinical target organ damage, according to pre-specified secondary endpoints.

Procedures

All the following measurements were obtained at pre-randomization and at 6 months.

Office- and 24 hour ambulatory- blood-pressure measurements

Office BP was assessed after 5 min of rest in the sitting position using validated oscillometric semiautomatic devices (Omron 705IT, Kyoto, Japan) with appropriate sized cuffs, between 8-10 A.M. and before taking any antihypertensive drug. Three measurements spaced by 1–2 min were averaged to determine the final office BP values.

A 24h-ambulatory blood-pressure monitoring (ABPM) registry was obtained by validated Spacelabs-90207 devices and suitable sized cuffs. The monitoring started at around 8-10 A.M. of a working day, with ambulatory BP readings obtained at 20-min intervals throughout both awake and asleep periods. A good technical quality recording (minimum 80% of valid readings) was required for a 24h-ABPM registry to be evaluable.

Urine albumin excretion

The urine albumin excretion (UAE) was recorded by standard methods (using a turbidimetric method) and determined as the average of the ratio of concentration of albumin to creatinine in two spot first-morning void urine samples collected on separate days. Urine creatinine was measured by an enzymatic modified Jaffe' reaction (CREA; Roche Diagnostics) using the Hitachi Modular System Analyzer (Roche Diagnostics). Microalbuminuria was defined following the European Society of Hypertension Guidelines (14), as an albumin-creatinine ratio of 30-300 mg/g.

Arterial stiffness

Carotid-femoral pulse wave velocity (cfPWV) was evaluated by noninvasive applanation tonometry on carotid and femoral arteries (Sphygmocor® device, AtCor Medical, Sydney, Australia) (15). The values of two valid consecutive measurements (all performed in a single centre by the same trained nurse) were averaged at each visit. cfPWV was computed as the distance travelled by the pulse wave divided by pulse wave transit time. Travel distance was measured to the nearest centimetre with an external tape measure over the body surface. The transit time was determined as the time difference between the feet of carotid and femoral arterial waveforms gated to ECG. Arterial stiffness was defined by cfPWV > 10 m/s (14). In addition, two other measurements were used to assess arterial stiffness. From derived central waveforms, data were obtained for augmentation pressure, and central augmentation index (AIx-75 bpm) was defined as the ratio of augmentation pressure to pulse pressure and normalized to a heart rate of 75 beats per min to minimize the influence of heart rate.

Carotid ultrasound

An ultrasound examination of both carotid arteries (left and right) to measure intima-media thickness (IMT) and/or the presence of plaques was performed in all patients. Intima-media thickness was measured at three different sites, i.e. common carotid artery (1 cm distal to bulb), bulb and internal carotid (1 cm proximal to bulb) by an Esaote® ultrasound device and specific measurement software. The final value for IMT was the average of these six measures. Carotid ultrasound was abnormal if wall thickening (IMT >0.9 mm) or plaques were found (14).

Echocardiographic measurements

All echocardiography examinations were performed and read by one single experienced physician blinded to randomization and all other information. Cardiac dimensions and wall thickness were measured according to standard recommendations (14,16). Left ventricular internal dimension and wall thickness were measured at end-diastole and left ventricular mass was calculated and indexed to body surface area to give left ventricular mass index (LVMI). The diagnosis of left ventricular hypertrophy (LVH) was considered if LVMI was > 115 g/m^2 (men) and > 95 g/m^2 (women). Alterations in diastolic dysfunction (17) were assessed by pulsed-wave tissue Doppler recordings of peak early (E-wave) and late (A-wave) diastolic flow velocities and the E/A ratio, as well as by recordings of the lateral portion of the mitral annulus to obtain the early diastolic e'-wave velocity. The mitral inflow E velocity to tissue Doppler e' (E/e') ratio was used as an index of LV filling. Left atrial volume and area indexes were also measured.

Statistical analyses

Variables following normal distribution are summarized as mean ± S.D. or as median (IQR, interquartile range) if asymmetrically distributed, and categorical data are presented as frequencies and percentages. Comparisons of baseline characteristics of patients in one treatment strategy arm or another were carried out by unpaired *t*-tests in continuous normally distributed data, by nonparametric either Wilcoxon or Mann-Whitney tests in asymmetrically distributed data, or by χ^2–test in categorical data. Between-group comparisons of changes in BP or in preclinical target organ damage markers were performed by using generalized linear models adjusted by respective baseline values. When the independent variable was the change in different markers of target organ damage, the variation of 24h-systolic BP was also included in the model.

For this analysis, both UAE and AIx-75 bpm were log-transformed because of skewed distribution. Spearman's "rho" was calculated for correlations. A two sided p value of ≤0.05 was considered statistically significant. Ordinary statistical methods were performed with statistical package SPSS for Windows version 22.0 (Cary, North Carolina, USA).

RESULTS

In total, 24 randomized patients had complete data on ABPM and target organ damage at baseline and final visit (6 months) and were analyzed. Thirteen patients were allocated in the spironolactone group and 11 patients underwent RDN. Mean age was 63.5 ± 7.5 yr and 63% were males. Mean office SBP and DBP were 170.1 ± 20.4 mmHg and 91.8 ± 12.0 mmHg, respectively. Baseline clinical characteristics and BP values in both groups are shown in Table 1. As observed, there were no statistically significant differences between groups (p=NS for all comparisons). All included diabetic patients had type 2 diabetes mellitus. In diabetic patients, baseline glycosylated hemoglobin was 7.1% ± 0.9 and 7.8% ± 0.8 (p=0.2) for the RDN and the spironolactone groups, respectively. Baseline antihypertensive treatment was also comparable between groups (Supplementary Table S1). All patients in RDN group and 92% of patients in spironolactone group received renin-angiotensin system blockers. According to the pre-specified protocol but attending to ethical and safety reasons, there were few changes in the baseline antihypertensive regimen and no statistically significant differences between groups were observed. Many of these changes consisted of a dosage adjustment, and in any case spironolactone was added to any patient of the RDN group. In table 2 baseline data on markers of preclinical target organ damage, both as quantitative and qualitative variables, are compared between groups. Baseline UAE and

24h-PP showed a trend towards a higher value in the spironolactone group. No other between-groups difference was observed regarding preclinical organ damage.

As previously reported (13), spironolactone was superior to RDN in reducing both 24h-SBP (-17.9 mmHg [95% CI -30.9 to -4.9 mmHg]; p=0.01) and 24h-DBP (-6.6 mmHg [95% CI -12.9 to -0.3]; p=0.04). Changes in markers of preclinical target organ damage at 6 months are compared between both treatment groups in Table 3. For the whole cohort, UAE (p= 0.013) and arterial stiffness, as assessed by cfPWV (p=0.001) and 24h-PP (p=0.001) showed a statistically significant decrease at 6 months with respect to baseline values. As seen, these changes mostly occurred in the spironolactone group. In this regards, individual changes in albuminuria within each treatment group are shown in Figure 1. However, these differences lost statistical significance after adjusting for both respective baseline values and the variation of 24h-SBP (data not shown). As shown in Figure 2, changes in UAE correlated with changes in 24h-SBP in the whole cohort ($r = 0.713$; $r^2 = 0.508$; $p < 0.001$).

Changes in additional echocardiographic parameters as regards systolic and diastolic function and left ventricle and atrium parameters, were also analyzed. As shown in Table S2, no statistically significant between-group differences were found.

DISCUSSION

In patients with RH, we have found a reduction in preclinical target organ damage, specifically in albuminuria, in those who received spironolactone as add-on therapy. As these results show, spironolactone is not only superior to renal denervation in lowering blood pressure, but also in organ damage regression. At 6 months there were no changes in other markers of preclinical target organ damage in the DENERVHTA study, except

a trend towards a reduction in arterial stiffness when assessed by PP, but not with PWV or AIx.

The main goal in treating RH is to minimize target organ damage and, therefore, to reduce cardiovascular morbidity and mortality. Recently, two of the approaches to treat RH that are under the spotlight of clinical research are sympathetic RDN, a minimally invasive non-pharmacological procedure with controversial results as for efficacy in lowering BP (10,18), and spironolactone, an old antihypertensive drug with quite good results shown in several studies in RH (11-13). Beyond efficiency to reduce BP, the effect of these treatments on markers of target organ damage has separately been reported, although most of the studies are non-randomized and results are generally inconclusive or are lacking sufficient consistency. A few studies have assessed their effect on UAE. In 59 RH patients with either micro- or macroalbuminuria who underwent RDN in a non-controlled study a significant reduction in UAE was shown, which correlated with changes in office SBP but not with changes in ambulatory SBP (19). Moreover, Verloop et al. (20) reported the effects of RDN on target organ damage in 54 RH patients, showing no change in UAE after 12 months. As regards spironolactone, its addition in both non-RH (21) and RH (22) patients produced a significant decrease in albuminuria as compared to placebo, although the relationship with changes in BP is not shown in these reports. Regarding arterial stiffness, there are some studies that analyze its variation after treatment with RDN or spironolactone in patients with RH. In the non-controlled study of Verloop et al. (20) assessing the effects of RDN, contrary to expectations, it was found an increase in PWV at 12 months and no change in AIx-75 bpm. On the other hand, several trials have explored the effects of mineralocorticoid receptor blockers on arterial stiffness. In patients with early chronic kidney disease treated with a renin-angiotensin system blocker, the addition of

spironolactone led to a reduction in both PWV and AIx-75 bpm even after adjusting for BP variation[21]. In another study (23), the addition of eplerenone in patients with uncontrolled hypertension reduced arterial stiffness as evaluated according to the cardio-ankle vascular index, and this reduction was not associated with changes in BP. Even less information is available on changes in carotid wall thickness with both these treatments, and none in patients with RH. In fact, we have found a single study on the effect of RDN in carotid IMT in 12 patients (24), showing no change, and only two small studies showing a reduction of their progression in hemodialysis patients (25) and a regression in patients with primary aldosteronism but not in those with essential hypertension (26), when treated with spironolactone. Finally, several studies have analyzed the effect of both treatments on cardiac ultrasound parameters. In RH patients, some studies have shown an improvement in echocardiographic parameters after RDN, mostly those related to LVMI or diastolic function parameters, but none of them are randomized controlled trials (27,28). On the other hand, when spironolactone was given as add-on therapy in patients with RH in comparison to dual renin-angiotensin system blockade it resulted in a decrease in LVMI after adjustment for ambulatory BP, as reported by Azizi et al. (29) in a well-conducted trial. One possible explanation for not finding a decrease in LVMI in our study may be the fact that, although in both groups there is around a 75% of patients with left ventricular hypertrophy, the absolute values of LVMI are relatively low in this cohort. This could explain why the decrease in LVMI is not statistically significant.

Overall, reliable information on the effect of RDN or spironolactone on preclinical target organ damage in patients with RH is scarce. Though both treatments seem to have a positive effect in improving organ damage, irrespective or not of the variation on BP, there is no trial comparing both treatment strategies. Here we report for the first time the

effect of spironolactone and RDN as add-on therapy in patients with RH on several markers of preclinical target organ damage in a randomized controlled trial. We have found a higher decrease in albuminuria in the spironolactone group, as compared to patients who underwent RDN. Even though we found a significant correlation between changes in albuminuria and variation of BP, in fact our results ($r^2 = 0.508$) mean that half of the variation in log UAE is due to something other than changes in 24h-SBP. Thus, a specific role for spironolactone beyond its effect on lowering BP cannot be discarded. Whatever the reason is, the important finding is that spironolactone as add-on treatment in patients with RH lowers both BP and preclinical organ damage more than RDN, and based on this it seems reasonable to hypothesize that these patients have better cardiovascular prognosis, although longer term studies are needed to confirm it. We found no significant changes regarding other secondary endpoints, i.e. PWV, ecochardiographic parameters or carotid IMT. One possible reason is the time interval that has been evaluated. Six months is probably too short a time to observe changes in these markers of organ damage. In fact, the expected time for an intervention produce changes is more than 6 months for albuminuria and arterial stiffness and more than 12 months for carotid IMT and echocardiographic measurements (14). Moreover, the high variability of some of these markers could account for the lack of other between-group differences. Other limitation in the present study might be not using cardiac magnetic resonance imaging to determine left ventricular mass and other cardiac measurements, considered more reliable than echocardiography. Moreover, it is well-known that until now no study allows to assess the effectiveness of the RDN procedure and the extent and duration of renal denervation effect are unknown. Finally, we must be aware of the somewhat small number of patients included in this trial. As strengths, we must emphasize that investigators performing echocardiographic, carotid and cfPWV

measurements were the same for all patients, and they were blinded to the allocation treatment group. Moreover, most of the patients in both groups remained on the same baseline pharmacological treatment during follow-up, as reported (13). In the present study the BP-lowering effect was determined by using 24-hour ambulatory BP measurements, reinforcing the reliability of the findings. Finally, we cannot rule out different results in other clinical settings such as patients with mild hypertension or by using other renal denervation catheters, other devices to measure arterial stiffness or other mineralocorticoid receptor blockers. Nor can we rule out possible side-effects on long-term spironolactone therapy, not observed in this 6-month follow-up period.

In conclusion, after 6 months of added-on treatment there is an improvement in preclinical target organ damage in RH patients treated with spironolactone but not in those undergoing RDN.

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Figure titles and legends

Figure 1.

Title: Individual changes in albuminuria from baseline to 6 months in (A) renal denervation group and (B) spironolactone group.

Legend: **Log-UAE,** log-transformed urine albumin excretion.

Figure 2.

Title: Correlation between changes at 6 months (**Δ)** of 24h-SBP and Δ urine albumin excretion (UAE).

Legend: **SBP**, systolic blood pressure; **UAE**, urine albumin excretion

Table 1. Patients' demographics and baseline laboratory and blood pressure characteristics.

Variable	Renal denervation (n=11)	Spironolactone (n=13)	*p*
Clinical characteristics			
Age, y	61.9 ± 6.6	64.9 ± 8.2	0.35
Gender, males, n (%)	6 (55)	9 (69)	0.68
Body mass index, kg/m^2	33.7 ± 7.4	30.6 ± 3.6	0.23
Diabetes, n (%)	4 (36)	8 (62)	0.41
Dyslipidemia, n (%)	11 (100)	11 (85)	0.48
Previous CVD, n (%)	2 (18)	3 (23)	0.64
Duration of HT (yr)	13.6 ± 6.9	14.2 ± 7.7	0.82
Antihypertensive drugs, n	4.3 ± 0.8	3.9 ± 0.6	0.13
Office and Ambulatory BP			
office-SBP (mm Hg)	168.0 ± 13.8	171.2 ± 16.8	0.74
office-DBP (mm Hg)	89.6 ± 12.8	90.2 ± 16.1	0.79
24h-SBP (mm Hg)	149.2 ± 6.9	155.4 ± 9.9	0.09
24h-DBP (mm Hg)	81.3± 8.8	80.9 ± 9.7	0.93
24h-PP (mm Hg)	68.0 ± 6.9	74.5 ± 10.6	0.09
daytime-SBP (mm Hg)	152.6 ± 7.9	158.9 ± 9.4	0.10
daytime-DBP (mm Hg)	83.8± 10.5	83.4 ± 9.3	0.92
daytime-PP (mm Hg)	68.5 ± 6.8	75.5 ± 9.7	0.06
nighttime-SBP (mm Hg)	141.9 ± 11.4	147.7 ± 15.5	0.32
nighttime-DBP (mm Hg)	75.7± 8.8	75.9 ± 11.7	0.98

nighttime-PP (mm Hg)	66.2 ± 9.2	71.9 ± 14.2	0.26

BP, blood pressure; **CVD,** cardiovascular disease; **DBP**, diastolic blood pressure; **HT**, hypertension; **PP**, pulse pressure; **SBP**, systolic blood pressure.

Data given as mean±SD or percentages.

Table 2. Baseline data of markers of preclinical target organ damage.

Variable	**Renal denervation (n=11)**	**Spironolactone (n=13)**	***p***
UAE (mg/g)*	9.0 [6.8; 104.1]	28.8 [19.1; 222.1]	0.07
Micro- or macroalbuminuria, n (%)	4 (36)	7 (54)	0.44
eGFR (mL/min/1.73m^2)	75.9 ± 20.0	81.3 ± 16.1	0.47
Renal dysfunction†, n (%)	3 (27)	1 (8)	0.30
AI-75 bpm (%)*	20.0 [15.0; 28.5]	24.0 [21.0; 26.5]	0.46
24h-PP (mmHg)	68.0 ± 6.9	74.5 ± 10.6	0.09
cfPWV (m/s)	12.4 ± 2.9	13.4 ± 2.9	0.42
Arterial stiffness‡, n (%)	8 (73)	11 (92)	0.32
Carotid IMT (mm)	0.67 ± 0.05	0.66 ± 0.09	0.82
IMT >0.9 mm and/or plaques, n (%)	7 (64)	10 (83)	0.37
LVMI (g/m^2)	121.6 ± 36.6	117.6 ± 21.8	0.74
LV Hypertrophy, n (%)	8 (73)	9 (75)	1
E/e'	10.1 ± 2.3	10.0 ± 4.3	0.97

E/e' ≥ 13, n (%)	1 (9)	1 (8)	1

*Data given as median (p25; p75). Remaining data are given as mean ± SD or percentages; †eGFR<60 mL/min/1.73m^2; ‡ cfPWV >10 m/s.

AIx-75 bpm, augmentation index normalized to a heart rate of 75 beats per minute, **cfPWV**, carotid-femoral pulse wave velocity; **E/e'**, E-wave/annular e' velocities ratio; **eGFR,** estimated glomerular filtration rate by CKD-EPI formula; **IMT,** intima-media thickness; **LV**, left ventricular; **LVMI**, left ventricular mass index; **PP**, pulse pressure; and **UAE**, urinary albumin excretion.

Table 3. Changes in markers of preclinical target organ damage at 6 months.

Variable	All patients (n=24) Change at 6 months Mean (95% CI)	*p* value	Renal denervation (n=11) Change at 6 months Mean (95% CI)	Spironolactone (n=13) Change at 6 months Mean (95% CI)	*p*-value ΔRDN vs. ΔSpironolactone
Renal damage					
UAE (mg/g)	-82.7 (-158.5; -7.0)	0.013	-23.8 (-104.5; 56.9)	-87.2 (-164,5; -9.9)	0.028
Carotid artery					
carotid IMT (mm)	0.01 (-0.04; 0.05)	0.719	-0.29 (-0.05; 1.29)	-0.01 (-0.13; 0.05)	0.396
Arterial stiffness					

cfPWV (m/s)	-1.03 (-1.61; -0.44)	0.001	-0.7 (-1.5; 0.2)	-1.3 (-2.2; -0.5)	0.259
AIx-75 bpm (%)	-1.11 (-5.87; 3.64)	0.417	-0.4 (-7.6; 6.9)	-1.8 (-8.4; 4.9)	0.768
24h-PP (mmHg)	-8.3 (-12.8; -3.8)	0.001	-2.1 (-7.9; 3.7)	-13.5 (-18.8; -8.2)	0.006
Echocardiographic parameters					
LVMI (g/m^2)	-2.0 (-14.4; 10.6)	0.750	1.83 (-16.6; 20.2)	-5.41 (-23.0; 12.2)	0.561
E/e'	-0.47 (-1.59; 0.65)	0.393	-0.32 (-2.0; 2.58)	-0.61 (-2.6; 2.0)	0.795

Δ, change; **AIx-75 bpm,** augmentation index normalized to a heart rate of 75 beats per minute; **cfPWV**, carotid-femoral pulse wave velocity; **E/e',** E-wave/annular e' velocities ratio; **IMT**, intima-media thickness; **LVMI**, left ventricular mass index; **PP,** pulse pressure; **UAE**, urinary albumin excretion

Figure 1

(A) Renal denervation group **(B) Spironolactone group**

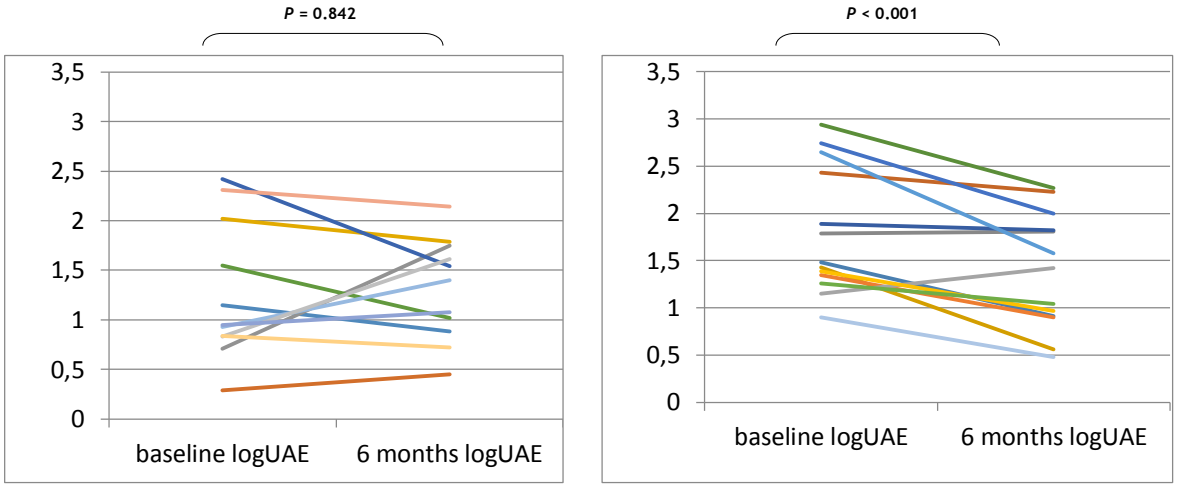

Figure 2

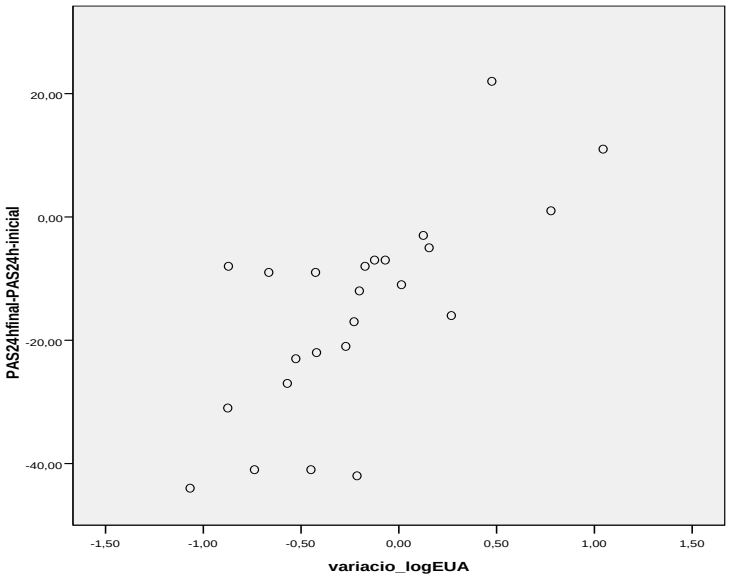

Table S1. Characteristics of antihypertensive treatment at baseline.

Variable	Renal denervation (n=11)	Spironolactone (n=13)
RAS blockers, n (%)	11 (100)	12 (92)
α-blockers, n (%)	6 (55)	5 (39)
β-blockers, n (%)	6 (55)	10 (77)
Calcium channel blockers, n (%)	10 (91)	9 (69)
Diuretics*, n (%)	11 (100)	13 (100)
Centrally acting drugs, n (%)	2 (18)	1 (8)

*****Other than mineralocorticoid-receptor blockers.

RAS, renin-angiotensin system.

Table S2. Changes in echocardiographic parameters.

Variable	Renal denervation (n=11) Change at 6 months Mean (95% CI)	Spironolactone (n=13) Change at 6 months Mean (95% CI)	*p* value
DIASTOLIC FUNCTION and LEFT ATRIUM PARAMETERS			
E-wave velocity (cm/s)	-1.3 (-10.4; 7.9)	-3.1 (-11.9; 5.7)	0.769
A-wave velocity (cm/s)	-1.0 (-10.1; 8.1)	-13.3 (-22.0; -4.5)	0.057
E/A velocity ratio	0 (-0.1; 0.1)	0.1 (0; 0.3)	0.192
Annular e' lateral velocity (cm/s)	0.4 (-1.2; 1.9)	-0.1 (-1.6; 1.4)	0.675
E/e' velocity ratio	-0.3 (-2.0; 2.6)	-0.6 (-2.6; 2.0)	0.795
LA volume index	-0.8 (-5.7; 4.1)	-0.4 (-5.0; 4.3)	0.903
LA area index	-0.4 (-1.7; 1.0)	-0.1 (-1.4; 1.2)	0.791
SYSTOLIC FUNCTION and LEFT VENTRICLE PARAMETERS			
LVMI (g/m^2)	1.8 (-16.6; 20.2)	-5.4 (-23.0; 12.2)	0.561
LV mass/height$^{2.7}$ ($g/m^{2.7}$)	2.3 (-7.2; 11.8)	-3.2 (-12.3; 5.9)	0.398
IVSTd (mm)	-0.1 (-1.1; 0.9)	0 (-1.0; 0.9)	0.942
PWTd (mm)	0.2 (-0.8; 1.2)	-0.2 (-1.2; 0.7)	0.546
LVIDd (mm)	-0.1 (-3.7; 3.5)	-1.9 (-5.3; 1.5)	0.451
LVIDs (mm)	-0.8 (-4.5; 2.9)	-2.4 (-6.0; 1.1)	0.524
LVEF (%)	2.8 (-2.8; 8.4)	1.8 (-3.5; 7.2)	0.801
RWT (cm)	0 (-0.1; 0.1)	0 (-0.1; 0.1)	0.995
GLS (%)	0 (-2.1; 2.1)	-0.7 (-2.6; 1.2)	0.635

GLS, global longitudinal strain; **IVSTd**, end-diastolic interventricular septum thickness; **LA**, left atrial; **LV**, left ventricular; **LVEF**, left ventricular ejection fraction; **LVIDd**, end-diastolic left ventricular internal diameter; **LVIDs**, end-systolic left ventricular internal diameter; **LVMI**, left ventricular mass index; **PWTd**, left ventricular end-diastolic posterior wall thickness; **RWT**, relative wall thickness.