

# Spironolactone versus sympathetic renal denervation to treat true resistant hypertension: results from the DENERVHTA study – a randomized controlled trial

Anna Oliveras<sup>a</sup>, Pedro Armario<sup>b</sup>, Albert Clarà<sup>c</sup>, Laia Sans-Atxer<sup>a</sup>, Susana Vázquez<sup>a</sup>, Julio Pascual<sup>a,\*</sup>, and Alejandro De la Sierra<sup>d,\*</sup>

See editorial comment on page 1701

**Objective:** Both renal denervation (RDN) and spironolactone have been proposed for the treatment of resistant hypertension. However, they have not been compared in a randomized clinical trial. We aimed to compare the efficacy of spironolactone versus RDN in patients with resistant hypertension.

**Methods:** A total of 24 patients with office SBP at least 150 mmHg and 24-h SBP at least 140 mmHg despite receiving at least three full-dose antihypertensive drugs, one a diuretic, but without aldosterone antagonists, were randomized to receive RDN or spironolactone (50 mg) as add-on therapy. Primary endpoint was change in 24-h SBP at 6 months. Comparisons between treatment groups were performed using generalized linear models adjusted by age, sex, and baseline values.

**Results:** Spironolactone was more effective than RDN in reducing 24-h SBP and 24-h DBP: mean baseline-adjusted differences between the two groups were  $-17.9$  mmHg (95%CI  $-30.9$  to  $-4.9$ );  $P=0.010$  and  $-6.6$  mmHg (95%CI  $-12.9$  to  $-0.3$ );  $P=0.041$ , for 24-h SBP and 24-h DBP, respectively. As regards changes in office blood pressure, mean baseline-adjusted differences between the two groups were  $-12.1$  mmHg (95%CI  $-29.1$  to  $5.1$ );  $P=0.158$  and of  $-5.3$  mmHg (95%CI  $-16.3$  to  $5.8$ );  $P=0.332$ , for office SBP and office DBP, respectively. Otherwise, the decrease of estimated glomerular filtration rate was greater in the spironolactone group; mean baseline-adjusted difference between the two groups was  $-10.7$  ml/min per  $1.73$  m<sup>2</sup> (95%CI  $-20.1$  to  $-1.4$ );  $P=0.027$ .

**Conclusion:** We conclude that spironolactone is more effective than RDN to reduce 24-h SBP and 24-h DBP in patients with resistant hypertension. Therefore, spironolactone should be the fourth antihypertensive drug to prescribe if deemed well tolerated in all patients with resistant hypertension before considering RDN.

**Keywords:** ablation, hypertension, renal denervation, resistant hypertension, spironolactone

**Abbreviations:** ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DENERVHTA, DENERVación en HiperTensión Arterial; eGFR, estimated glomerular filtration rate; HR, heart rate; RDN, renal denervation

## INTRODUCTION

Resistant hypertension is a matter of big magnitude, not only because of its prevalence, estimated around 5–15% when nonadherence to or inadequate treatment and white-coat hypertension are discarded [1–4], but also because of the associated cardiovascular risk [5,6]. It is well known that subclinical target organ damage [5], major cardiovascular outcomes and mortality [6] occur more often in patients with resistant hypertension than in those with controlled hypertension. In the last few years, the advent of a nondrug minimally invasive treatment, that is, sympathetic renal denervation (RDN), opened great expectations about its possible usefulness as a treatment modality in this group. Initial promising results [7,8], reporting 25–30 mmHg decreases in office SBP at 6 months, favoured the widespread use of this technique. However, more recently the randomized controlled trial Symplicity HTN-3 failed to demonstrate a significant blood pressure (BP) decrease as compared with the ‘sham’ control group [9]. Meanwhile, several reports had begun to focus on the possible important role of spironolactone, an antagonist of aldosterone receptors, in the treatment of resistant hypertension [10]. Thus, in the Addition of Spironolactone in Patients with Resistant Arterial Hypertension trial [11] spironolactone as an add-on treatment showed decreases in

Journal of Hypertension 2016, 34:1863–1871

<sup>a</sup>Hypertension Unit, Nephrology Department, Hospital Universitari del Mar, Barcelona IMIM (Hospital del Mar Medical Research Institute), Spanish Research Network REDINREN (RD12/0021/0024), <sup>b</sup>Internal Medicine Department, Vascular Risk Area, Hospital Moisès Broggi, Consorci Sanitari Integral, <sup>c</sup>Vascular Surgery Department, Hospital Universitari del Mar, Barcelona IMIM (Hospital del Mar Medical Research Institute) and <sup>d</sup>Internal Medicine Department, Hospital Mútua Terrassa, University of Barcelona, Barcelona, Spain

Correspondence to Anna Oliveras, MD, PhD, Hospital del Mar, Nephrology Department, Hospital Universitari del Mar, Barcelona IMIM (Hospital del Mar Medical Research Institute), Passeig Marítim 25-29, 08003 Barcelona, Spain. Tel: +34 93 2483483; fax: +34 93 2483373; e-mail: aoliveras@hospitaldelmar.cat

\*Julio Pascual and Alejandro De la Sierra contributed equally to this work, and are the colast authors.

Received 3 April 2016 Revised 23 May 2016 Accepted 30 May 2016

J Hypertens 34:1863–1871 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

DOI:10.1097/HJH.0000000000001025

both office SBP (14.6 mmHg) and 24-h SBP (10.6 mmHg), that were significantly higher than corresponding reductions in the respective control groups, in which baseline antihypertensive treatment was maintained. More newly, 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 resistant hypertension.

Therefore, we designed a randomized clinical trial to evaluate the efficacy of radiofrequency RDN in patients with resistant hypertension, as compared with the addition of spironolactone to the therapeutic regimen at baseline.

## METHODS

### Study design and patients

The DENERVHTA (DENERVación en HiperTensión Arterial) study is a prospective, multicentre, open-label, randomized, controlled trial, which enrolled patients from October 2012 to April 2015 at three tertiary care centres specialized for hypertension diagnosis and management, all in Catalonia, Spain. The trial was approved by the local institutional Ethics Committees in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants. Patients aged at least 18 years and 80 years or less with an office SBP at least 150 mmHg and a 24-h SBP at least 140 mmHg despite a prescribed therapeutic schedule with an appropriate combination of three or more full-dose antihypertensive drugs, including a diuretic, and maintained for the last 3 months, were eligible to participate in the trial. All patients underwent renal artery imaging, either a MRI or a computed tomography, to ensure anatomical eligibility. Recruited patients for this study required to have a suitable anatomy for RDN to ensure that it was affordable with satisfactory technical outcomes. Therefore, only patients with main renal arteries with a diameter wide enough (4 mm) to enable denervation were included. Branches were also denervated when technically possible according to this diameter. Exclusion criteria included inability to perform either imaging tests; secondary hypertension, with appropriate tests being performed according to investigator criteria (with special focus on primary aldosteronism, that was ruled out by both plasmatic aldosterone and renin activity determinations after stopping interfering medications as well as by computed tomography or MRI); estimated glomerular filtration rate (eGFR) less than 45 ml/min/1.73m<sup>2</sup>; patients currently on treatment with an aldosterone receptor blocker or who had previously received one of such class of drugs and had been withdrawn because of lack of efficacy and/or adverse effects; patients unlikely compliant with treatment (assessed according to Haynes–Sackett test [13]). Other exclusion criteria comprised prerandomization serum potassium level at least 5.5 mmol/l, pregnant women, significant valvular heart disease, or the occurrence of a major vascular event (myocardial infarction, unstable angina, or stroke) within 6 months prior to study enrolment.

After eligibility confirmation, all patients were randomized (in a 1 : 1 ratio) to either receive sympathetic RDN plus baseline antihypertensive treatment or spironolactone plus

baseline antihypertensive treatment. The randomization sequence was generated by computer and stratified by centres using randomized blocks of small size and permutation of treatments within each block. For patients allocated to the spironolactone arm, this drug was started in a morning daily dosage of 25 mg with forced titration to 50 mg after 1 month. Physicians were encouraged to maintain study participants of both treatment groups on the initial antihypertensive drug regimen throughout the study, although for safety reasons the protocol provided the possibility of modifications when strictly required. The open design of the study allowed us to realize that the decrease in BP could be higher in the spironolactone group. Therefore, we performed an interim analysis that confirmed this suspicion. Based on this analysis, the inclusion of patients was definitely discontinued before planned and the results of patients randomized until then were analysed, which are presented here.

### Procedures

A 24-h ABPM registry and laboratory tests were obtained at prerandomization and at 6 months. Validated Spacelabs-90207, (Issaquah, Washington, USA) devices and suitable sized cuffs were used for 24-h ABPM. The monitoring started at around 8–10 a.m. of a working day, with ABP readings obtained at 20-min intervals throughout both awake and asleep periods. These periods were defined according to the sleep and wake-up times reported by the patients during the monitoring day. A good technical quality recording (minimum 80% of valid readings) was required for a 24-h ABPM registry to be evaluable. Moreover, office BP was measured during the outpatient visits at baseline and at 2 weeks, 1, 3, and 6 months after randomization. BP was assessed after 5 min of rest in the sitting position using appropriate sized cuffs, between 0800–1000 h before taking any antihypertensive drug, through validated oscillometric semiautomatic devices (Omron 705IT, Kyoto, Japan). Three measurements spaced by 1–2 min were averaged to determine the final office BP values. Self-reported adverse events were also recorded at each visit. As prespecified in the protocol, serum potassium levels were closely monitored in patients who received spironolactone, concretely in 2 weeks after having started or increased the dose of the drug. For safety reasons, there were extra BP measurements or laboratory tests throughout the study according to medical discretion. BP measurements were performed by trained nurses, and the investigator responsible of the inclusion of each patient attended the medical outpatient visits, recording any adverse event and making decisions as prespecified in the protocol in accordance with BP measurements and analyses results.

### Sympathetic renal denervation

All RDN procedures were performed in one single interventional centre by one specifically trained interventionalist alone, who had previous experience with the system before the study started. The single electrode radiofrequency Symplicity catheter (Medtronic, Galway, Ireland) was used in all procedures, performed 2 ± 1 week after

randomization. As recommended [14], 4–6 applications of low-power (~8W) radiofrequency energy were delivered to each renal artery, in a helical pattern from distal to proximal within the main renal artery, with a distance between ablation sites near 5 mm. Before and during the procedure, patients were administered analgo-sedation and intravenous heparin. Intraarterial nitroglycerine was administered through renal guide and heparinized saline was continuously flushed during the procedure.

## Outcomes

The primary endpoint was the between-group comparison of mean changes in ambulatory 24-h SBP from baseline to 6 months.

Secondary endpoints included mean changes in all other BP and heart rate parameters from baseline to 6 months as assessed by ambulatory and office measurements. Safety outcomes, that is, acute renal failure (doubling of serum creatinine or dialysis requirement), hyperkalaemia (serum potassium levels persistently higher than 5.8 mmol/l despite implementation of lowering potassium measures) as well as mean changes in eGFR [as measured by using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula] were evaluated. A decrease of at least 25% of the baseline eGFR was considered clinically relevant. Self-reported adverse events from baseline to 6 months were also recorded.

## Statistical analyses

We did the statistical analyses on the ‘intention-to-treat’ population, using the last observation carried forward. Ordinary statistical methods were performed with statistical package SPSS for Windows version 21.0 (Cary, North Carolina, USA). Briefly, variables following normal distribution are summarized as mean  $\pm$  SD or as median (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 Mann–Whitney test in asymmetrically distributed data, or by  $\chi^2$ -test in categorical data. Between-group comparisons of changes in BP and heart rate measurements as well as laboratory parameters were performed by using generalized linear models adjusted by age, sex, and respective baseline values. A change was considered significant if the two-side  $\alpha$  level was 0.05 or less.

## RESULTS

Total 38 patients with suspected resistant hypertension on the basis of office BP were screened for eligibility. Eleven patients were not randomized because of 24-h SBP less than 140 mmHg ( $n = 7$ ), unsuitable renal artery anatomy ( $n = 3$ ) and consent withdrawal ( $n = 1$ ). In all 27 patients fulfilled inclusion criteria and were randomized after confirming they had office SBP at least 150 mmHg and 24-h SBP at least 140 mmHg. Thirteen patients were allocated to the RDN group and 14 patients were allocated to the spironolactone group. In the RDN group, two patients did not undergo the procedure because of refusal. One patient in the

spironolactone group was also excluded from this analysis because of no 24-h ABPM data (Fig. 1). In total, 24 patients were analysed. Mean age was  $63.5 \pm 7.5$  years and 63% were men. Mean office SBP was  $170.1 \pm 20.4$  mmHg and mean office DBP was  $91.8 \pm 12.0$  mmHg. Mean 24-h ambulatory SBP and DBP were  $152.5 \pm 9.0$  mmHg and  $81.1 \pm 9.1$  mmHg, respectively. Main baseline clinical characteristics and BP values of patients are shown in Table 1. As regards these baseline characteristics, there were no statistically significant differences between groups ( $P = NS$  for all comparisons). The proportions of patients in each pharmacological drug class are shown in Table 2.

One patient in the spironolactone group was withdrawn 8 weeks after randomization because of hyperkalaemia, according to the prespecified safety procedures. This patient underwent a 24-h ABPM registry and laboratory analyses at the early final visit and was included in the ‘intention-to-treat’ analyses. Patients randomized to RDN group received a median (interquartile range) of 10 (10; 11) renal artery ablations. As abovementioned, the RDN consisted on four to six applications of low-power radiofrequency energy delivered to each renal artery (82% of the patients received 10–12 applications in total). These ablations successfully followed a circumferential pattern from distal to proximal within the main renal artery in all cases, with a distance between ablation sites near 5 mm, as recommended by the device company and according to consensus documents [14].

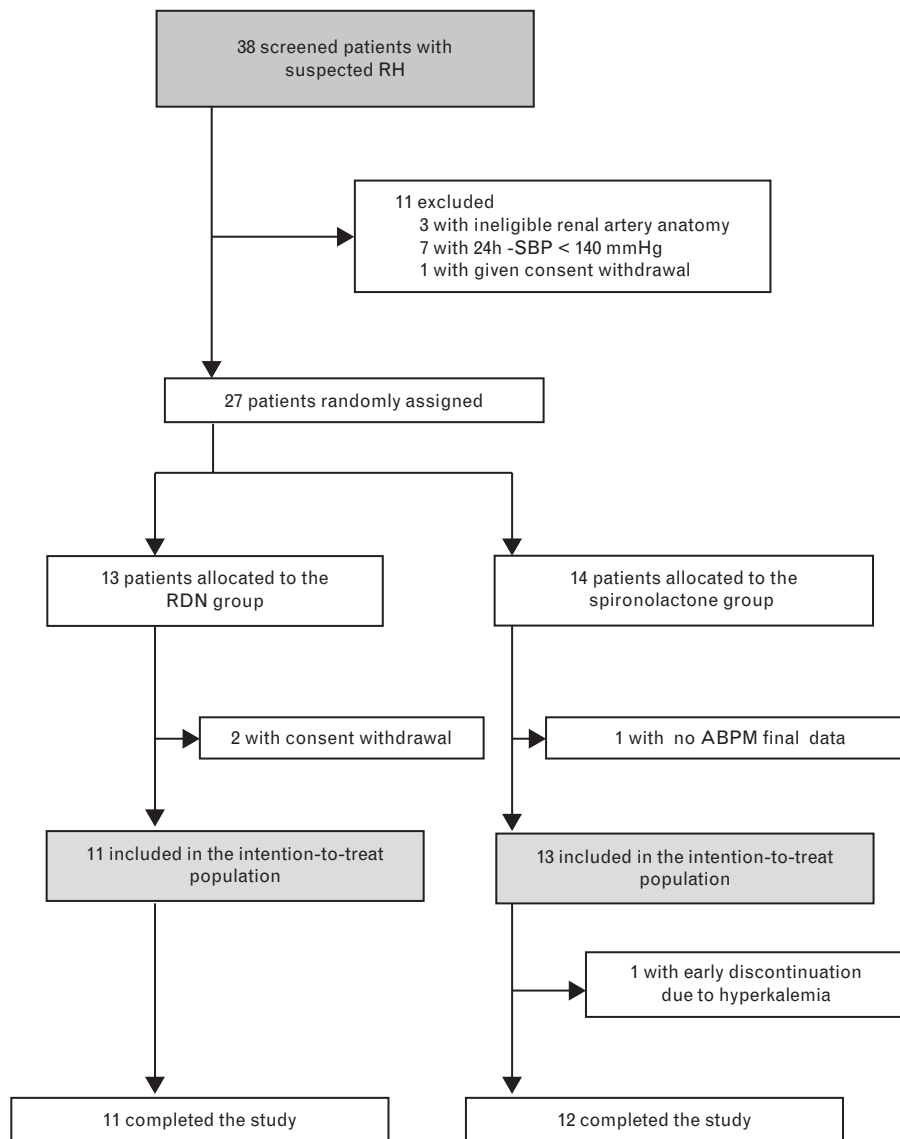
## The 24-h ambulatory blood pressure

After 6 months, the mean reduction in 24-h SBP was significantly superior in the spironolactone group than in the RDN group. After adjusting by age, sex, and baseline 24-h SBP, a mean difference between the two groups of  $-17.9$  mmHg (95% CI  $-30.9$  to  $-4.9$  mmHg);  $P = 0.01$  (Table 3) was observed. Similarly, there was a statistically significant more substantial decrease in 24-h DBP in the spironolactone group, with a mean difference between the two groups of  $-6.6$  mmHg (95% CI  $-12.9$  to  $-0.3$ );  $P = 0.04$ . All changes in BP parameters and comparisons between groups are summarized in Table 3. Similar results were observed as for daytime SBP and DBP. As regards nighttime BP, changes in both SBP and DBP were not significantly different between groups, although there was a trend toward a higher decrease in night-time SBP in the spironolactone group ( $P = 0.06$ ). Finally, mean baseline-adjusted pulse pressure significantly decreased in the spironolactone group as compared with the RDN group in 24 h, daytime and night-time periods.

Moreover, 24-h SBP control rate, that is, the percentage of patients with 24-h SBP less than 130 mmHg at 6 months, was 53.9% in the spironolactone group, but no patient in the RDN group achieved a 24-h SBP lower than 130 mmHg ( $P = 0.006$ ).

## Office blood pressure and heart rate

As regards office SBP and DBP and office and ambulatory heart rate, no statistically significant differences were observed in the between-group comparisons (Table 3). Moreover, patients with controlled office SBP



**FIGURE 1** All patients that gave signed consent are summarized with status through month 6. A total of 27 study participants were randomized. Three patients (two in the RDN group, one in spironolactone group) missed the primary endpoint. The remaining 24 patients were included in the intention-to-treat analyses. ABPM, ambulatory blood pressure monitoring; RDN, renal denervation; RH, resistant hypertension.

(<140 mmHg) were 36% ( $n = 4$ ) in the RDN group and 62% ( $n = 8$ ) in the spironolactone group, with no statistically significant differences between groups ( $P = 0.4$ ).

**Safety issues**

Table 4 shows the main changes in potassium and renal laboratory parameters. Mean baseline-adjusted variation of eGFR at 6 months showed a decrease in the spironolactone group that was significantly more profound than changes in eGFR in the RDN group. Thus, the mean baseline-adjusted difference between the two groups (spironolactone versus RDN) in eGFR was  $-10.7 \text{ ml/min/1.73m}^2$  (95% CI  $-20.1$  to  $-1.4$ ),  $P = 0.03$ . On the other hand, baseline-adjusted serum potassium levels significantly increased in the spironolactone group in comparison to changes in RDN ( $P < 0.001$  for the mean baseline-adjusted difference between groups) as

expected. One patient in the spironolactone group withdrew the study because of hyperkalemia, as prespecified in the protocol. Another patient could not reach the dose of 50 mg of spironolactone because of high serum potassium levels. As regards changes in eGFR, the number of patients with at least a 25% decrease of baseline eGFR at 6 months was 0 and 5 (39%) in the RDN and spironolactone groups, respectively. Otherwise, no other serious adverse event was observed. Thus, acute renal failure did not develop in any patient.

As regards other adverse events, mild groin hematoma ( $n = 3$ ) and transient symptomatic hypotension ( $n = 3$ ) developed in five patients in the RDN group, and one patient in the spironolactone group reported hyponatremia, muscle cramps, and transient symptomatic hypotension. None patient withdrew the study because of these adverse events.

**TABLE 1. Patient demographics and baseline laboratory and blood pressure characteristics**

Variable	Renal denervation (n = 11)	Spironolactone (n = 13)	P
<b>Clinical characteristics</b>			
Age (year)	61.9 ± 6.6	64.9 ± 8.2	0.4
Sex, males, n (%)	6 (55)	9 (69)	0.7
Caucasian, n (%)	11 (100)	11 (85)	0.4
BMI (kg/m <sup>2</sup> )	33.7 ± 7.4	30.6 ± 3.6	0.2
Abdominal circumference (cm)	113.7 ± 13.5	108.7 ± 9.8	0.3
Current cigarette smokers, n (%)	5 (46)	4 (31)	0.7
Diabetes, n (%)	4 (36)	8 (62)	0.4
Dyslipidaemia, %, n (%)	11 (100)	11 (85)	0.5
Previous CVD, n (%)	2 (18)	3 (23)	0.6
Duration of hypertension (year)	13.6 ± 6.9	14.2 ± 7.7	0.8
Antihypertensive drugs, n	4.3 ± 0.8	3.9 ± 0.6	0.1
<b>Laboratory parameters</b>			
Serum creatinine (μmol/l)	86.7 ± 28.9	81.3 ± 13.2	0.6
eGFR (ml/min per 1.73 m <sup>2</sup> ) <sup>a</sup>	74.6 (54.8; 91.2)	85.0 (68.1; 95.8)	0.5
Serum potassium (mmol/l)	4.1 ± 0.4	4.0 ± 0.6	0.9
UAE (mg/g) <sup>a</sup>	9.0 (6.8; 104.1)	28.8 (19.1; 222.1)	0.1
Microalbuminuria, n (%)	4 (36)	7 (54)	0.4
<b>BP values</b>			
<i>Ambulatory BP</i>			
24-h SBP (mmHg)	149.2 ± 6.9	155.4 ± 9.9	0.1
24-h DBP (mmHg)	81.3 ± 8.8	80.9 ± 9.7	0.9
24-h PP (mmHg)	68.0 ± 6.9	74.5 ± 10.6	0.1
24-h HR (bpm)	63.3 ± 6.3	68.2 ± 9.4	0.2
Daytime SBP (mmHg)	152.6 ± 7.9	158.9 ± 9.4	0.1
Daytime DBP (mmHg)	83.8 ± 10.5	83.4 ± 9.3	0.9
Daytime PP (mmHg)	68.5 ± 6.8	75.5 ± 9.7	0.1
Daytime HR (bpm)	66.5 ± 7.8	70.5 ± 10.0	0.3
Night-time SBP (mmHg)	141.9 ± 11.4	147.7 ± 15.5	0.3
Night-time DBP (mmHg)	75.7 ± 8.8	75.9 ± 11.7	0.9
Night-time PP (mmHg)	66.2 ± 9.2	71.9 ± 14.2	0.3
Night-time HR (bpm)	57.3 ± 6.4	62.9 ± 9.7	0.1
<i>Office BP</i>			
Office SBP (mmHg)	168.0 ± 13.8	171.2 ± 16.8	0.6
Office DBP (mmHg)	89.6 ± 12.8	90.2 ± 16.1	0.9
Office PP (mmHg)	78.4 ± 17.0	81.1 ± 18.8	0.7
Office HR (bpm)	67.1 ± 10.6	67.7 ± 12.7	0.9

BP, blood pressure; bpm, beats per minute; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, heart rate; HT, hypertension; PP, pulse pressure; UAE, urinary albumin excretion.

<sup>a</sup>Data given as median (IQR). Remaining data are given as mean ± SD or percentages.

## Changes in antihypertensive treatment

Overall there were no between-group statistically significant differences as regards changes in the number or dose of drugs ( $P=0.5$ ). Total 73% of patients in the RDN group ( $n=8$ ) and 64% ( $n=9$ ) of patients in the spironolactone group remained with the same baseline antihypertensive regimen at 6 months.

**TABLE 2. 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 <sup>a</sup> , n (%)	11 (100)	13 (100)
Centrally acting drugs, n (%)	2 (18)	1 (8)

RAS, renin-angiotensin system.

<sup>a</sup>Other than mineralocorticoid-receptor blockers.

## DISCUSSION

The main finding of the DENERVHTA study is that in patients with true resistant hypertension, the addition of spironolactone to the baseline antihypertensive drug therapy reduced 24-h SBP at 6 months more than RDN. Correspondingly, the 6-month 24-h SBP control rate was significantly higher in the group with added spironolactone. The percentage of patients who needed to add or to withdraw antihypertensive drugs was similar in both groups, and there were no differences as for the occurrence of self-reported adverse events. As regards office BP, the decrease in both SBP and DBP from baseline to 6 months did not significantly differ between groups.

Initial studies showed a decrease of 26–28 mmHg in office SBP at 6 months after RDN in patients with resistant hypertension [15,16]. However, they suffered from various shortcomings, including the absence of a control group with a different therapeutic strategy beyond the maintenance of basal drug treatment, or the lack of 24-h ABP assessment, a more reliable tool to evaluate changes in BP than office BP. Further on, the quite well designed

**TABLE 3. Mean baseline-adjusted changes in office and ambulatory blood pressure variables at 6 months**

Variable	Renal denervation (n = 11)	Spironolactone (n = 13)	Mean baseline-adjusted difference (95% CI) between the two groups at 6 months (spironolactone versus RDN)	P
	Change ( $\Delta$ ) at 6 months, mean (95% CI)	Change ( $\Delta$ ) at 6 months, mean (95% CI)		
24-h SBP (mmHg)	-5.7 (-14.8 to 3.4)	-23.6 (-31.9 to -15.3)	-17.9 (-30.9 to -4.9)	0.01
24-h DBP (mmHg)	-3.7 (-8.2 to 0.9)	-10.2 (-14.4 to -6.1)	-6.6 (-12.9 to -0.3)	0.04
24-h PP (mmHg)	-1.7 (-7.2 to 3.9)	-13.9 (-19.0 to -8.8)	-12.3 (-20.1 to -4.4)	0.004
24-h HR (bpm)	0.7 (-2.2 to 3.7)	3.6 (0.9 to 6.2)	2.8 (-1.4 to 7.0)	0.2
Day SBP (mmHg)	-5.7 (-14.8 to 3.4)	-23.6 (-31.9 to -15.3)	-17.9 (-30.8 to -4.9)	0.009
Day DBP (mmHg)	-3.0 (-7.4 to 1.5)	-9.8 (-13.9 to -5.8)	-6.9 (-13.0 to -0.7)	0.03
Day PP (mmHg)	-1.9 (-8.5 to 4.8)	-14.1 (-20.1 to -8.0)	-12.2 (-21.7 to -2.8)	0.01
Day HR (bpm)	0.4 (-3.4 to 4.1)	4.0 (0.6 to 7.4)	3.6 (-1.6 to 8.9)	0.2
Night SBP (mmHg)	-7.7 (-18.8 to 3.4)	-22.3 (-32.4 to -12.2)	-14.6 (-30.2 to 0.9)	0.06
Night DBP (mmHg)	-5.5 (-11.2 to 0.3)	-10.9 (-16.1 to -5.9)	-5.4 (-13.4 to 2.6)	0.2
Night PP (mmHg)	-2.5 (-8.2 to 3.3)	-11.5 (-16.7 to -6.2)	-9.0 (-17.0 to -1.0)	0.03
Night HR (bpm)	0.6 (-3.0 to 4.3)	3.3 (0.0-6.7)	2.7 (-2.5 to 7.9)	0.3
Office SBP (mmHg)	-17.5 (-29.7 to -5.1)	-29.4 (-40.7 to -18.1)	-12.1 (-29.1 to 5.1)	0.2
Office DBP (mmHg)	-7.5 (-15.5 to 0.5)	-12.7 (-20.0 to -5.5)	-5.3 (-16.3 to 5.8)	0.3
Office PP (mmHg)	-10.4 (-19.6 to -1.2)	-18.5 (-26.9 to -10.1)	-8.1 (-20.8 to 4.7)	0.2
Office HR (bpm)	0.9 (-14.9 to 16.7)	11.7 (-1.9 to 25.3)	10.8 (-10.5 to 32.1)	0.3

BP, blood pressure; bpm, beats per minute; CI, confidence interval; HR, heart rate.

Symplicity HTN-3 study [9] where patients were randomized to RDN or to 'sham' procedure, failed to demonstrate between-group statistically significant differences in SBP decrease, neither when assessed by office BP nor by 24-h ABP recording. Other studies have compared RDN and 'sham' procedure [17] to treat patients with resistant hypertension and some trials have compared RDN versus adjusted antihypertensive drug treatment [18–20]. Taking together, as shown in a recent meta-analysis [21], although these studies suggested that RDN is superior to an appropriate pharmacological strategy, it becomes necessary further confirmation because of the high heterogeneity among study populations. As regards the role of spironolactone in the treatment of patients with resistant hypertension, the very recently published results from the PATHWAY-2 trial [12] have shown that the addition of spironolactone 25–50 mg is by far more effective to reduce home SBP than the addition of placebo, bisoprolol, or doxazosin in patients with resistant hypertension. Otherwise, some of the trials mentioned above comparing RDN and intensified pharmacological treatment [19,20] permitted or prespecified the inclusion of spironolactone as part of the

antihypertensive schedule in the pharmacological group of treatment. However, none of them planned a head-to-head comparison of RDN versus spironolactone as exclusive add-on therapy. Therefore we designed the DENERVHTA study to determine between-group differences in changes in 24-h SBP in patients randomized to receive RDN or the addition of spironolactone to the antihypertensive drug treatment scheduled at that time. To our knowledge, this is the first randomized clinical trial that compares head-to-head two different concrete treatments added to the previous antihypertensive drug regimen, that is, the addition of a single drug, spironolactone, or the addition of a device-based treatment, RDN. Furthermore, 24-h BP is considered the most reliable way to measure BP [22], and therefore we planned to evaluate changes in 24-h SBP as the primary endpoint. The results clearly favoured the addition of spironolactone to the baseline antihypertensive treatment when facing the challenge of reducing high BP and of achieving BP control in patients with resistant hypertension. Several factors may justify the higher BP reduction in the spironolactone group. The main reason may be that in our study, the therapeutic algorithm for the

**TABLE 4. Mean baseline-adjusted changes in renal function parameters at 6 months**

Variable	Renal denervation (n = 11)	Spironolactone (n = 13)	Mean baseline-adjusted difference (95% CI) between the two groups at 6 months (spironolactone versus RDN)	p
	Change ( $\Delta$ ) at 6 months, mean (95% CI)	Change ( $\Delta$ ) at 6 months, Mean (95% CI)		
Serum creatinine ( $\mu\text{mol/l}$ )	5.9 (-2.3 to 14.1)	14.9 (7.4–22.4)	9.0 (-2.5 to 20.4)	0.1
eGFR (ml/min per 1.73 m <sup>2</sup> )	-3.0 (-9.8 to 3.9)	-13.7 (-20.0 to -7.4)	-10.7 (-20.1 to -1.4)	0.03
Serum potassium (mmol/l)	-0.13 (-0.36 to 0.11)	0.81 (0.60–1.03)	0.94 (0.62–1.25)	<0.001

CI, confidence intervals; eGFR, estimated glomerular filtration rate; RDN, renal denervation.

spironolactone group forced its titration to 50 mg whenever possible. This higher dose was not used in the aforementioned studies, where the predefined dosage was 25 mg. In fact, the important role of spironolactone to achieve BP control in patients with difficult-to-treat or resistant hypertension has been increasingly acknowledged. In the previously referred PATHWAY-2 trial [12] almost 60% of patients achieved BP control when receiving spironolactone, a percentage very close to that found in our study, that is, 54%. According to the protocol of the DENERVHTA trial, secondary causes of hypertension, including primary aldosteronism, had been ruled out by appropriate studies. However, it has been admitted that many patients with resistant hypertension have an aldosterone excess, a dysregulation of either this hormone or the epithelial sodium channel, and even modestly elevated or nearly normal levels of aldosterone are believed to be inappropriately high and likely to contribute to a volume overload state in them [23,24]. In this way, it was previously shown in other trials [25,26] that the addition of spironolactone reduced office SBP by 24–25 mmHg in patients with resistant hypertension, irrespective of whether they had or not primary aldosteronism. In this DENERVHTA study we have found a decrease around 29 mmHg in office SBP, a quite similar BP reduction. We believe that it is very unlikely that undetected primary aldosteronism be the reason for the higher BP decrease in the spironolactone group.

As regards RDN, all procedures were carried out by the same interventionalist, to avoid intercentre and intracentre variability. The operator had received appropriate training in this treatment and acquired the skills on it, and had performed several procedures before initiating the trial. Observed changes in 24-h SBP in successively denervated patients in our study (*Supplementary material*, Figure S1, <http://links.lww.com/HJH/A645>) makes very unlikely that the operating learning curve affects the success of RDN procedures, which is in the line with the analysed results of the Symplicity HTN-3 trial [9]. Unfortunately, no reliable perioperative marker of successful RDN exists. Even though the number of ablations has failed to predict the BP response to RDN in some leading trials [19,20], the median of the number of shots in this study was 10, considered within the range with better decreasing BP results [27]. The decreases in both office and 24-h SBP are also quite similar to those achieved in other trials [28].

It is of note that differences between groups regarding the decreases on office BP values did not reach statistical significance. It appears that the white-coat phenomena is specially highly prevalent in patients with resistant hypertension, showing a reduction in office BP values that does not parallel to the 24-h BP decrease. In this line, results of three open RDN trials [29] indicate that the white-coat effect must drop by ~18 mmHg from baseline to final examination, implying that the alerting response almost completely disappears and suggesting that this effect could be mediated by renal nerves. This could at least partly explain the favourable results to RDN observed in the first studies, Symplicity HTN-1 and HTN-2, with main data referred to office BP [7,8]. Other authors have also reported no effect on ABP monitoring in patients with pseudoresistant hypertension, whereas a reduction in office BP to a similar extent to that of patients

with true resistant hypertension was observed [30]. Attending to other secondary endpoints, we have found a decrease of 7.7 mmHg in night-time SBP in the RDN group that was not significantly different from that in the aldosterone group. As we have pointed above, RDN appears to unmask the white-coat phenomena of some patients with resistant hypertension. Accordingly, the partial component of 'true' resistant hypertension in these patients could be reflected by the relatively higher drop in night-time BP. This was suggested to occur in the Symplicity HTN-3 trial [31] and could also be the explanation for our own results as regards night-time BP reduction.

There are some possible limitations to our study. One potential limitation is the relatively small size of the DENERVHTA study cohort. However, the publication of the results from the Symplicity HTN-3 trial [9] and the observation in our own trial that spironolactone appeared to be superior to RDN in decreasing BP, led to perform the corresponding interim analyses and to subsequently stop the inclusion of patients. Post hoc power sample size calculation with the current number of enrolled patients shows that considering that the difference in 24-h SBP lowering is 17 mmHg, with a bilateral  $\alpha$  error of 0.05, the statistical power is of 92% with an average SD of 13 mmHg. We must acknowledge that some at-risk patients, that is, those with low GFR or high baseline serum potassium were excluded in this study, which limits the advantage of spironolactone to a group of patients with certain clinical features. Anyway, we must remark that results are checked at 6 months; thereafter, it should be of interest to closely follow-up renal function and serum potassium levels and we cannot discard possible adverse results on that, neither the possibility of a poor long-term adherence to spironolactone. Another possible limitation is that we cannot strictly ensure therapeutic adherence even testing the Haynes–Sackett test to enter the study. However, we believe that this limitation is largely offset by the strict BP inclusion criteria, beyond the precise definition of resistant hypertension. Other strength of this trial is that patients maintained their baseline antihypertensive-drug regimen at least for 3 months prior to enrol the study, consequently ensuring a true resistance to pharmacological treatment. Finally, our results cannot be extrapolated to other clinical settings (such as patients with mild hypertension or worse renal function) or generalizable to other RDN catheters or devices or to other mineralocorticoid receptor blockers.

In conclusion, we have found that in patients with true resistant hypertension, the addition of 50 mg daily of spironolactone is more effective than RDN to reduce 24-h SBP and DBP at 6 months. In the light of these results, we believe that spironolactone should be considered as the fourth antihypertensive drug to prescribe if deemed well tolerated in all patients with diagnosed true resistant hypertension, even though it is mandatory to closely monitor renal function in these patients and carefully uptitrate the drug.

## ACKNOWLEDGEMENTS

The work was supported by the Spanish Health Authority: EC11–426. The funder had no role in study design;

collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

#### Investigators' list

Pedro Armario, MD; Francina Barbosa, MD; Angela Barrera, MD; Albert Clarà, MD; Alejandro de la Sierra, MD; Anna Faura, RN; Lidia González, MD; Tai Mooi Ho, RN; Omar Ibrik, MD; Carme Llorca, MD; Carmen Martín, RN; Meritxell Mellado, MD; Lluís Molina, MD; Anna Oliveras, MD; Julia Pareja, MD; Julio Pascual, MD; Carmen Roman, RN; Laia Sans, MD; Marta Serra, MD; Susana Vázquez, MD; Maria Vera, RN; Ernest Vinyoles, MD.

### Conflicts of interest

A.O. contributes to scientific advisory with Medtronic Ibérica, S.A. since February 2015. All the remaining authors declare no conflicts of interest.

Clinical Trial Registration – URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02039492

### REFERENCES

- Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension* 2011; 57:1076–1080.
- de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, *et al.* Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; 57:898–902.
- Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, *et al.* Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; 125:1635–1642.
- Calhoun DA, Booth JN 3rd, Oparil S, Irvin MR, Shimbo D, Lackland DT, *et al.* Refractory hypertension: determination of prevalence, risk factors, and comorbidities in a large, population-based cohort. *Hypertension* 2014; 63:451–458.
- de la Sierra A, Banegas JR, Oliveras A, Gorostidi M, Segura J, de la Cruz JJ, *et al.* Clinical differences between resistant hypertensives and patients treated and controlled with three or less drugs. *J Hypertens* 2012; 30:1211–1216.
- Sim JJ, Bhandari SK, Shi J, Reynolds K, Calhoun DA, Kalantar-Zadeh K, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. *Kidney Int* 2015; 88:622–632.
- Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, *et al.* Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373:1275–1281.
- Symplcity HTN-2 Investigators Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplcity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; 376:1903–1909.
- Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, *et al.*, SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014; 370:1393–1401.
- Pimenta E, Calhoun DA, Oparil S. Mechanisms and treatment of resistant hypertension. *Arq Bras Cardiol* 2007; 88:683–692.
- Václavík J, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, *et al.* Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomised, double-blind, placebo-controlled trial. *Hypertension* 2011; 57:1069–1075.
- Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, *et al.*, British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet* 2015; 386:2059–2068.
- Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? *Hypertension* 1980; 2:757–764.
- The Joint UK Societies' Consensus Statement on Renal Denervation for Resistant Hypertension. Caulfield M, de Belder M, Cleveland T, Collier D, Deanfield J, Gray H, *et al.* On behalf of the British Hypertension Society, the British Cardiovascular Intervention Society, the British Society for Interventional Radiology, National Institute for Clinical Outcomes Research, the British Cardiovascular Society, and the Renal Association. <https://www.nice.org.uk/guidance/IPG418>.
- Krum H, Schlaich MP, Sobotka PA, Böhm M, Mahfoud F, Rocha-Singh K, *et al.* Percutaneous renal denervation in patients with treatment-resistant hypertension: final 3-year report of the Symplicity HTN-1 study. *Lancet* 2014; 383:622–629.
- Esler MD, Böhm M, Sievert H, Rump CL, Schmieder RE, Krum H, *et al.* Catheter-based renal denervation for treatment of patients with treatment-resistant hypertension: 36 month results from the SYMPLICITY HTN-2 randomised clinical trial. *Eur Heart J* 2014; 35:1752–1759.
- Desch S, Okon T, Heinemann D, Kulle K, Röhnert K, Sonnabend M, *et al.* Randomised sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. *Hypertension* 2015; 65:1202–1208.
- Fadl Elmula FE, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, *et al.* Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014; 63:991–999.
- Rosa J, Widimský P, Toušek P, Petrák O, Čurila K, Waldauf P, *et al.* Randomised comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension* 2015; 65:407–413.
- Azizi M, Sapoval M, Gosse P, Gosse P, Chatellier G, Renal Denervation for Hypertension (DENERHTN) investigators. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. *Lancet* 2015; 385:1957–1965.
- Pancholy SB, Shantha GP, Patel TM, Sobotka PA, Kandzari DE. Meta-analysis of the effect of renal denervation on blood pressure and pulse pressure in patients with resistant systemic hypertension. *Am J Cardiol* 2014; 114:856–861.
- Siu AL, U.S. Preventive Services Task Force Recommendation Statement. Screening for high blood pressure in adults. *Ann Intern Med* 2015; 163:778–786.
- Judd E, Calhoun DA. Management of resistant hypertension: do not give up on medication. *Nephrol Self Assess Program* 2014; 13:57–63.
- Lohmeier TE, Liu B, Hildebrandt DA, Cates AW, Georgakopoulos D, Irwin ED. Global- and renal-specific sympathoinhibition in aldosterone hypertension. *Hypertension* 2015; 65:1223–1230.
- Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003; 16:925–930.
- Dahal K, Kunwar S, Rijal J, Alqatahni F, Panta R, Ishak N, Russell RP. The effects of aldosterone antagonists in patients with resistant hypertension: a meta-analysis of randomised and nonrandomised studies. *Am J Hypertens* 2015; 28:1376–1385.
- Briasoulis A, Bakris G. Renal denervation after SYMPLICITY HTN-3: where do we go? *Can J Cardiol* 2015; 31:642–648.
- Hameed MA, Pucci M, Martin U, Watkin R, Doshi S, Freedman J, *et al.* Renal denervation in patients with uncontrolled hypertension and confirmed adherence to antihypertensive medications. *J Clin Hypertens (Greenwich)* 2016; 18:565–571.
- Howard JP, Nowbar AN, Francis DP. Size of blood pressure reduction from renal denervation: insights from meta-analysis of antihypertensive drug trials of 4121 patients with focus on trial design: the CONVERGE report. *Heart* 2013; 99:1579–1587.
- Mahfoud F, Ukena C, Schmieder RE, Cremers B, Rump LC, Vonend O, *et al.* Ambulatory blood pressure changes after renal sympathetic denervation in patients with resistant hypertension. *Circulation* 2013; 128:132–140.
- Bakris GL, Townsend RR, Liu M, Cohen SA, D'Agostino R, Flack JM, *et al.*, SYMPLICITY HTN-3 Investigators. Impact of renal denervation on 24-h ambulatory blood pressure. Results from SYMPLICITY HTN-3. *J Am Coll Cardiol* 2014; 64:1071–1078.



## Reviewer's Summary Evaluation

### Reviewer 1

The study is strengthened by its randomized, prospective design and lengthy follow-up. Study weaknesses include it being done as an unblinded study and its relatively small cohort size. The study is novel in directly comparing the antihypertensive efficacy of spironolactone versus renal nerve denervation (RND) and the findings are provocative in finding the former so much better. It does add to the literature in indicating the superiority of pharmacologic approaches and highlights the relatively modest effects of RND, at least in this cohort.

### Referee 2

This small randomized, open label study suggests that in patients with resistant hypertension spironolactone (50 mg/day) is more effective in reducing ambulatory blood pressure at 6 months follow-up compared to renal denervation using a single electrode ablation catheter. These findings support the utility of aldosterone antagonists as a fourth line treatment for resistant hypertension but also highlight the need to closely monitor renal function. Whether sufficient renal denervation was actually achieved in the interventional group could not be determined. Ongoing sham-controlled studies with multi-electrode devices will clarify whether more complete denervation can match the blood pressure-lowering efficacy of spironolactone.